PRACTICAL ORGANOTHERAPY

The Internal Secretions in General Practice

HARROWER

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THE INTERNAL SECRETIONS IN GENERAL PRACTICE

BY

HENRY R. HARROWER, M. D., F. R. S. M. (Lond.)

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THE HARROWER LABORATORY

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SECTION I

INTRODUCTION

For more than ten years I have been studying the glands of internal secretion with increasing interest, and in explanation of the work of a "laboratory of applied endocrinology" now known as "The Harrower Laboratory" which was established in the foot-hill city of Glendale, eight miles north of Los Angeles, California, in February, 1918, I must preface this book with a few remarks.

My interest in the endocrine glands grew out of some work which I did in 1908-9 on metabolism, acidemia and, especially, the urinary acidity. I wrote a number of papers during that period, some of which appeared in prominent medical journals in America and Europe. In asking myself why faulty metabolism and deficient cell chemistry was brought about I could not but consider the "regulators of metabolism," as Noel Paton calls them—the hormones of the glands of internal secretion.

After several years of casual study in Chicago, I went abroad for more than two years, during which time I had opportunity to visit several of the leading students in this field, in many different countries. My enthusiasm was considerably increased by what I saw and heard, and it was not long before I was convinced that we were far behind our European, and especially our French, colleagues. I have since kept in touch with these men, and in 1915-6 succeeded in establishing the *Association for the Study of Internal Secretions,* a body of physicians and investigators whose object is to further and correlate the work of many widely separated students of endocrinology. The Association's bulletin, *"Endocrinology,"* is a splendid and comprehensive review of the literature and advances in this important study.*

For years I had been impressed with the extreme importance

* The above Association will welcome cooperation from interested physicians. The present President (Dr. Lewellys F. Barker, Baltimore), or Secretary (Dr. F. M. Pottenger, Title Insurance Bldg., Los Angeles), will be pleased to correspond with those who desire to know more about the work and aims of the *A. S. I. S.* While I am not now actively promoting this Association, as its originator and a charter member, I am glad to pass on a word about the excellent service it is rendering to medicine, and especially about the journal mentioned above, which is a more than satisfactory return for the annual dues of five dollars.—H. R. H.

of glandular therapy. I had spent much time and effort to collate data on organotherapy, which was published in book form—"Practical Hormone Therapy: A Manual of Organotherapy for Practitioners"—in London, in 1914, by Bailliere, Tindall & Cox. I found out some of the wonderful things that were being done in the treatment of endocrine disease; and soon found myself wondering why so much attention was paid to obvious thyroid, adrenal, pituitary or gonad disease, when the functions of these glands are of such prime importance to the body that the slightest derangement of their hormone production must in the nature of things exert a more or less decided influence on the body. In other words I began to see the necessity of studying the minor, functional ductless glandular disorders, and the enthusiasm engendered by these studies has never waned for an instant. The matter will be given further consideration in many chapters of this book.

The Relations of the Endocrine Glands. The next logical step was to investigate the effects that certain endocrine dysfunction had on the other internal secretory organs; and it was soon very clear that *to treat a thyroid disorder just because it was obviously of thyroid origin was to ignore a fundamental principle which often has resulted in failure.* If a cretin or myxedematous individual really has an insufficient production of the thyroid hormones, and these internal secretions not only regulate many important functions of the body, but also the endocrine function of many or all of the other members of the internal secretory system, how is it possible not to have associated disorders due to the resulting associated dyscrinism? This means that we must consider the work of the body as a whole—of the endocrine glands as a series, and when we do this we will find that in the hypothyroidism just mentioned there is also a very well defined series of disturbances in the pituitary gland, the sex glands, the adrenals and, in fact, in the whole ductless glandular system. Hence the cretin must have more than attention to the thyroid insufficiency. *The same applies to every form of dyscrinism.* As has been stated editorially in the *New York Medical Journal* (July 20, 1918): "All (the endocrine glands) are so closely bound to each other that a disturbance in one will throw out of gear or out of action all of the others. . . . It is for this reason that in conditions thought to have origin in this form of disturbance gland medication, organotherapy, contemplates the giving of the extracts of many glands."

Here, then, was my job. To work out these interrelations from a clinical and therapeutic standpoint; and to facilitate the treatment of pluriglandular disorders by suitable pluriglandular therapy. This is the chief aim of the writer and object of this laboratory. And the results which have accrued in two short years are little short of amazing.

"Stock" and "Special" Formulas. In considering how to put this laboratory on a satisfactory and self-supporting basis, I decided in favor of building a business with certain organotherapeutic products in order that the profit derived from their sale might maintain the institution and that, as it grows, opportunities might be afforded to develop the suggestions of colleagues who, like myself, have had more or less intangible ideas which have been difficult or impossible of materialization because of limited finances or facilities. I also felt that the community of interests that would result from this effort would automatically further the ideal which I started out to materialize.

Having made this decision, the most natural way to start seemed to be to prepare a number of pluriglandular formulas which I had been in the habit of prescribing or recommending to my medical friends, and ask these friends to use them if they appeared reasonable. These "Stock Formulas" are given and their therapeutic possibilities are briefly discussed in the following pages, and your favorable consideration of them is solicited.

The next development of the work of this laboratory was the production from time to time of small experimental quantities of various organotherapeutic preparations for colleagues; and already this phase of our work bids fair to accomplish much in the way of broadening organotherapy. As I have said, this was the real underlying reason for deciding to begin operations. Such "Special Formulas" as may be ordered from day to day are worked out with or without my own suggestions as required. These formulas are made in smaller quantities than manufacturing pharmacists care to consider—only 300 suffices for a minimum batch, and I have occasionally made still less—and are modified from time to time as it seems advisable. Thus some very useful combinations already have been developed and it is a source of great encouragement to me to be able also to submit here a number of these "S. F.'s" with suggestive clinical indications and other data.

The Character of These Products. Wherever possible the accepted pharmacopeial methods of standardization are followed. For instance the thyroid "extract" contains the prescribed percentage of organically united iodine as required in the U. S. P. IX. Every effort is made to ensure effective desiccations, and I feel that from the standpoint of therapeutic efficacy, at least, the preparations of this laboratory are not excelled, even in France where the practical application of organotherapy is still far ahead of us.

Aside from the care in production and standardization, there is another very important matter to which I must call attention. We have no secret formulas. No camouflage on the labels or in the literature. We do not even use proprietary or trade names. There are no indications upon the labels and no enclosures in the

packages.* Every effort is made to be as honorable and professional as possible; yet despite this no one of the stock pluriglandular formulas from this laboratory is passed by the Council of Pharmacy and Chemistry. A number of them were submitted, but they failed to measure up to the Council's standards, not in so far as ethical standards are concerned, but for the following reasons: "Each of the mixtures contains one ingredient or more, which is neither recognized in the U. S. Pharmacopeia nor admitted to New and Non-official Remedies." This means that a glandular extract that has not reached this stage of acceptation and has been included in these lists is inadmissible. In fact in the same letter Professor Puckner, from his presumably large clinical experience, states that "there is no evidence that many of these organs have any value whatever when administered by the mouth or in any other way." This I deny as vehemently as I know how. I cannot gainsay the evidence of my own experience, nor can I ignore the numerous statements made to me personally and in writing. Further, there is plenty of evidence in current medical literature to support any reasonably minded physician in the use of, say, desiccated placenta, pancreas substance or even a sperm-bearing extract from the interstitial cells of Leydig from the testes.

The other reason for judging these stock formulas as inadmissible is this: "In the light of our knowledge the administration of gland mixtures in the host of conditions enumerated is irrational and on a par with the use of the shotgun mixtures once in vogue." From my own standpoint, as well as that of many others, I am glad to say this position is altogether invalid. First of all, "a host of conditions," indeed follows derangements of the endocrine functions merely because so many factors are dependent upon the proper endocrine balance. Secondly, there is a physiological principle with which Professor Puckner is probably not acquainted which regulates the capacity of those organs which are dependent upon hormone stimuli, to pick up from the blood the well-named "chemical messengers" which they need and in the proportion that they need them. (See "A Hypothesis of Hormone Hunger," page 27.) We must recall, too, that the blood contains all the hormones we know about and probably many more, as well as the opsonins, the agglutinins, the bacteriolysins, the cells, the platelets, the salts, and so on. A "shot-gun mixture" indeed; yet the body manages to make its selections very satisfactorily. Pluriglandular therapy is more rational than mono-glandular therapy, as experience has shown a thousand times and will continue to show. The subject is more fully dis-

* With two exceptions: A card in packages of *Caps. Amylo-Trypsin Co.* (No. 12) the statement on which is quoted elsewhere in this book and clinical suggestions to physicians in the package of *Liquor Hypophysis, U. S. P.* (No. 16).

cussed in another section. In the meantime we are trying to be as honorable and frank as we can, and I personally believe that I have the right to pass my own judgment and to do as I please in the matter. Whether others agree with me or not is for them to decide. *If it is a matter of results and the patient's best interests, the pluriglandular idea is a great advance in organotherapy.* I confess that my patients, my colleagues and the friends of this laboratory are only interested in *results* and they are not worried about the ineligibility or the "shot gun" character of the remedy.

We are making the very best preparations available. The contents are standardized when possible, the dosage is accurate, the combinations are based upon long experience, and time after time the use of these pluriglandular stock formulas has succeeded when presumably indicated single extracts had been used without anything like the good results obtained later.

Finally, if there is a single constructive suggestion which will enable us to modify for the better the formulas, the labels, the literature or the distribution of the products of The Harrower Laboratory, it will be accepted and put into execution as early as possible; *and such suggestions will be gratefully appreciated* by the writer.

Publications from This Laboratory. For a number of years I have been thinking about endocrine matters and from time to time I have read a paper or published an article on some subject in which I was particularly interested. In addition to this I have written a number of books, to which it may be well to call attention here.

A Monthly Journal on Organotherapy. Quite the most practical literature which is sent out from this laboratory is *The Organotherapeutic Review,* a small, pocket-size, monthly journal which is intended to review the advances in practical endocrinology and, in particular, to keep the profession in touch with the progress in the laboratory. This journal is eagerly read by many hundreds of physicians, who have come to look forward to its visits and many of whom confess that they are in the habit of slipping it into the pocket to be read from cover to cover during an O. B. case or at some convenient time.

The *Review* contains editorial articles by the writer on practical subjects in this field, a number of brief abstracted or translated articles, an occasional case history with suitable comment is published under the heading "The Monthly Clinic"—a feature of the journal which has called forth much friendly comment because it takes up diagnostic as well as therapeutic matters—and a Correspondence Department in which questions pertaining to clinical endocrinology are answered. This little journal will be sent to any physician each month without charge, on request.

"Practical Hormone Therapy." This book is a comprehensive study of the literature on organotherapy. It was published the

month war was declared, by Bailliere, Tindall & Cox of London. It has been called "the most complete and easily read book on this interesting subject" and consists of 508 pages, 36 chapters and a bibliography of nearly 1,000 references. Each of the important chapters has been in the hands of a recognized authority in the manuscript. For instance, Dr. Eugene Hertoghe, of Antwerp, reviewed the chapter on Thyroid; Sir Edward Schaefer, of Edinburgh, the chapter on the Pituitary; Prof. Paul Carnot, of Paris, the chapter on the Liver; Dr. Howard A. Kelly, of Baltimore, the chapter on the Ovary, and so on. There is no book at all like it in English, and despite the fact that nearly five years have elapsed since its publication it is today the best work on organotherapy in English. The price is $4.50, postage 20 cents. It is referred to again in Section II, Chapter I, and a copy will be sent on approval to any interested physician on request to The Harrower Laboratory.

"The Internal Secretions in General Practice." This consists of twenty papers and addresses on the subject, which includes much practical information on various phases of endocrinology. It is published by the Chicago Medical Book Company at $2.75. The supply is about exhausted, but possibly another edition will be printed before long.

"Outlines of Organotherapy." A concise, "boiled-down" outline of the whole subject, originally published in 1918 at $1.50. The essential contents of this book have been further revised and concentrated and constitute the first part of Section III of this book.

"The Adrenal Glands in Every-day Medicine." A collection of articles and abstracts on matters pertaining to the adrenals and indicating very conclusively the importance of this aspect of clinical medicine. Cloth bound, 64 pages, price $0.50. The cloth edition is nearly exhausted; but paper copies will be available, a copy of which will be sent free of charge to any interested physician.

Reprints and Back Numbers of the "Review." Without making a necessarily incomplete and indefinite list, it may be stated that the writer has numerous reprints on subjects relating to the internal secretions, as well as several back numbers (no complete sets) of *The Organotherapeutic Review.* Interested readers who care to address the Laboratory are welcome to as many of these as we have, and with no obligation.

The object of The Harrower Laboratory is to broaden medicine by developing the practically applicable things in the internal secretions. The chosen motto is, *"At YOUR Service."*

SECTION II

THE BASIS OF ORGANOTHERAPY

In this section, I have attempted to set down the fundamentals upon which present day organotherapy has been built. A knowledge of these ideas will give the reader a working understanding of the "why" and "how" of a much misunderstood but extremely valuable branch of therapeutic medicine.

SECTION II. CHAPTER 1

AN INTRODUCTION TO PRACTICAL ORGANOTHERAPY

Since the remote days of Hippocrates and Galen, and even of Brown-Sequard, the "sponsor of scientific organotherapy," the administration of preparations of animal organs has been used and discarded and used again. It is indeed a study of perennial interest and at no time has this subject attained so great and increasing a vogue as in these last few years.

There are four reasons for this that occur to me:

(1) Many experimental and clinical experiences have developed intelligible reasons for previous empirical practices;

(2) The production and standardization of glandular "extracts" (as they still are erroneously called) has attained a degree of excellence which far exceeds the work of previous years;

(3) The results following the use of organotherapeutic preparations sometimes are astonishing, even though other measures calculated to secure benefit have been tried again and again with little or no advantage.

(4) The development of the relation of the endocrine glands and of glandular synergisms has put a new aspect upon the whole subject which has attained practical value thru the application of *pluriglandular therapy.*

So far as I know there are some 54 books devoted to the internal secretions, the ductless glands, their pathology and other intimately allied subjects. Perhaps one-half of these are in the English language. Besides these books there are literally thousands of articles and reports on the therapeutics that this increasing knowledge has made possible. The study of organotherapy

or, as it is occasionally called, "hormone therapy," is daily gaining in scope and prestige.

Over two years of study in this field in Europe, with numerous visits to Paris—admitted to be the seat of learning in the science of *"opothérapie"*—Berlin, Brussels, Copenhagen, Amsterdam, London and Edinburgh, caused me to have a much greater respect for the subject which did not seem to be in particularly good repute when I left America in 1912. Many conversations with leading investigators in various phases of this subject, stimulated my interest. The literature was studied and a large file of clippings and reprints accumulated. Soon it appeared that much of this information was worth collating and I therefore prepared the manuscript for a book that would introduce interested readers to an extremely broad and fascinating subject which is passing from the stage of academic discussion to that of great value in every-day practice.

"No subject will prove more enthralling to the interested reader than the possibilities of hormone therapy, not only in the obvious disorders of the endocrine glands, but in many other diseases evidently amenable to treatment with their products. Nor will the interest wane when plausible theories have become tangible results; for the possibilities of this method are almost limitless; nor is its chemical basis dependent on the unsupported experiences of a few enthusiastic investigators."

Strangely enough, until the year 1914, there was no book in English which thoroughly covered the practical side of this subject, and it was my privilege to publish, just before the European war, a book called "Practical Hormone Therapy, a Manual of Organotherapy for General Practitioners."* In this book an attempt was made to collate in a more or less comprehensive fashion a majority of the most important facts relating to the many branches of the therapeutics made possible by the advance in our knowledge of the internal secretions and the organs producing them. This information covers such a wide field that the data was divided into 8 sections and 36 chapters. To facilitate the study of this old though still new subject, I added a glossary of terms, many of which are not yet in the medical dictionaries, so rapid has been the recent development of the subject an organotherapeutic dose-table and a series of bibliographies directing attention to no less than 793 references, the largest proportion of which directly concern the practical side of organotherapy.

The physician who is sufficiently interested to look up some of the bibliographic references to these various subjects, soon will be convinced of the reasonableness of many of the facts and suggestions which have been gathered there, and a much more

* This book may be obtained *on approval* from the Home Office of the Harrower Laboratory or any of its branch offices. The price is $4.50, postage extra.

complete series of references will be opened up to the student, for the bibliographies of the 800 articles indexed in "Practical Hormone Therapy" direct one to at least 4,000 additional communications! So much for the larger book which, I am glad to say, has been extremely well received and reviewed.

There is no doubt that many a difficult case will prove to be amenable to organotherapy, even after several other things have failed. I frequently find myself recalling experiences in my practice of years ago, that I am confident could have been simplified with practically no trouble—had I known what I now know about organotherapy. Ten years ago we did not have corpus luteum or pituitary extract to help us as wonderfully as they sometimes do now. It is hoped that the facts collated here may prove to be frequently serviceable to those into whose hands this book may come, and it will be a pleasure to hear from interested readers with criticisms, comments, experiences or requests for co-operation.

The section which follows comprises in truth the merest outlines. No attempt is made to explain the "why" and the "how." The essential physiologic basis or explanation is missing, as space is not available either for this information or for the numerous clinical experiences and reports which might supplement it, many of which may be found in my other books, or scattered throughout the literature of a dozen countries.

Here is offered the "real meat"—the boiled-down essentials of a subject which, according to Leonard Williams, "already unfolds before the astonished view of the seeing eye, a land of promise besides which the discoveries of Lister and Pasteur are destined to pale into honorable insignificance."

The real reason for preparing these outlines which were published in book form in 1918 under the title "Outlines of Organotherapy," is to serve the busy physician who "has no time for reading."

SECTION II. CHAPTER 2

THE ESSENTIAL FUNDAMENTALS

General Principles. The literature on organotherapy, especially that which has been published during the last ten years, is both vast and comprehensive; and marshals unnumbered facts which have placed this most ancient and altogether empiric form of therapeutics upon a scientific and up-to-date basis. The ductless glands have been studied with enthusiasm and thoroughness, and their importance is being more generally recognized because both the physiologists and the pathologists have definitely shown

us a part, at least, of their functions and connected their researches with many heretofore unsolved medical puzzles.

The status of the hormones, or the active principles obtained from certain glands of internal secretion secured from animals, and their use as remedial agents, has arrived at a place which reaches well beyond the laboratory of the physiologist. These active principles are undoubtedly specific substances, and some of them already have been isolated while others are obviously present although they have not yet been chemically separated. These substances have been given the convenient generic name "hormone" from the Greek, "I arouse," or "set in motion," and are now known to constitute a series of important chemical messengers by means of which the functions of the body are correlated.

Each hormone—sometimes an organ has the faculty of producing two or more hormones—has the inherent capacity of exciting to definite activity those cells for which it manifests a special affinity (In this connection note the chapter entitled, "A Hypothesis of Hormone Hunger."), and we are just beginning to appreciate the considerable importance which attaches to the normal production of these different hormones, as well as to the maintenance of the balance which is brought about by the action and interaction of these variously acting bodies.

While organotherapy is undoubtedly the oldest form of therapeutics, it has become the newest, for the good reason that the discovery of the hormones and their influence upon physiology has enabled the students of the past ten or fifteen years to give a reason for many clinical phenomena and thus establish the empirical procedure of Hippocrates, Galen and others of ancient and more modern times, upon a scientific and unquestioned basis.

Pharmacy has contributed its share to the growth of this phase of therapeutics, and much work has been done, especially in France and America, to produce therapeutically active as well as convenient preparations with which to apply in a practical way, the fundamental principles which have been laid bare.

These fundamental principles have been grouped under four chief heads under which the various organotherapeutic procedures may be classified conveniently. These forms of organotherapy are as follows:

1. *Substitutive.*
2. *Homostimulative.*
3. *Empirical.*
4. *Specific.*

A very brief consideration of each of these four forms of organotherapy will explain, in part, its scientific basis, and enable the interested reader to classify the animal extracts from a therapeutic standpoint, though in a somewhat different manner from the classification used in the subsequent pages in which the various organotherapeutic products are arbitrarily divided into three

classes according to their present popularity and therapeutic availability.

Substitutive Organotherapy. Properly prepared extracts of various glands supply a deficient physiological secretion of organs that correspond to those from which the extracts are made. The disorder may be due to absence, atrophy or functional inactivity of these organs, i. e., the production of their normal active principles has been reduced or stopped. A typical illustration of this category is the use of thyroid extract to replace the secretion which is missing, as in myxedema.

Homostimulative Organotherapy. The active principles of the internal secretory organs have a definite stimulative and restorative action upon the glands which correspond to those from which the extracts are made. It has been remarked by some French writers that organic extracts exert a regulative action upon the organs from which they are derived, not only favoring the restoration of their functions, but also of their normal anatomic structure. Hallion is prominent among these and his "law" briefly states this principle as follows:

"Extracts of an organ exert on the same organ an exciting influence which lasts for a longer or shorter time. When the organ is insufficient, it is conceivable that this influence augments its action, and, when it is injured, that it favors its restoration."

This principle is the basis of a large share of the value of organotherapy, and is represented quite typically by the use of bile in hepato-biliary insufficiency, or ovarian preparations in functional ovarian disorders.

Empirical Organotherapy. Certain animal extracts seem to influence certain clinical manifestations and as a result have come to be used without a definite and acceptable scientific basis. Examples of this form of organotherapy are the pituitary treatment of functional ovarian disorders, or the parathyroid treatment of paralysis agitans.

Incidentally as our appreciation of the intricacies of the endocrine relations grows, the empirical use of organotherapy will disappear and in its place we will put some other form. Already this may be true of the two examples just mentioned.

Specific Organotherapy. Finally, it has been found that extracts of certain organs exert a definite physiological influence, not by virtue of a homostimulative action, but by causing certain physiologic activity, or by counteracting some particular morbid symptoms not due to any change in the internal secretory action of the glands of the patient. The most decided and remarkable type of this class of organotherapeutic remedies is the extract of the posterior lobe of the pituitary body represented by *Liquor Hypophysis, U. S. P. IX* (Harrower), and its effect upon the uterine muscle, especially during labor.

Until quite recently it was the exception rather than the rule to find physicians having everyday recourse to the various hormone-bearing products, and while the administration of thyroid, adrenal and pituitary extracts is quite general, it should be remembered that their value was demonstrated before we knew that their activity was really in their contained hormones—before our present more extended knowledge of this subject had been attained.

It seems quite reasonable to presume that if, say, desiccated sheep's thyroids suffice to supply the lack brought about by thyroid insufficiency in the human, and that other glandular extracts serve to produce equally valuable therapeutic results, hormones produced in the glands of animals deserve to be more generally used as remedies; and the administration of the various specific glandular activators should become both a common and important factor in the practice of medicine.

It has been previously remarked that the administration of glandular extracts frequently serves as an actual stimulus to the work of the organ corresponding to that from which the extract was made. This may be accomplished by temporarily relieving certain overworked cell collections from the necessity of manufacturing their normal product, and thus allowing them rest, to recuperate and regain their lost or diminished function. Again, this action may be brought about by the specific influence which these hormones are presumed to exert upon the precursors of hormones in corresponding organs—it has been quite thoroughly established that the administration of secretin in addition to bringing about the activation of various digestive zymogens and their liberation from the pancreas, liver and intestine, definitely favors the production of an increased quantity of the precursor of secretin (prosecretin) in the duodenum itself, as well as causing an increase in the blood supply to that particular part. In other words, the ingested hormones also may be "made over" or used again, just as bile is reused by the liver after its alimentary service has been accomplished. Another equally important field of usefulness for the hormones is to supply immediately to the system substances for which it is craving as, for example, the use of the dynamogenic principles which regulate the so-called "adrenal system" and which are deficient in asthenic, run-down states, or ovarian extract in the disorders which follow the artificial menopause, etc.

If it is possible to procure from animals the substances which serve to activate certain of their functions, and by introducing them into the human body, to accomplish for the patient what these were intended to have done for the animal, is there not a most reasonable philosophy and foundation for the more general application of hormone therapy?

As Leonard Williams, of London, remarked in the preface to

his book, "Minor Maladies": "I believe that the serious study of what are called 'minor maladies' will lead to the prevention and forestalling of many serious diseases. Still more earnestly do I believe that the study of the whole field of the internal secretions will enable us to detect and correct morbid tendencies with a degree of success which has been denied to the older methods. The microbe—the seed—has ruled the immediate past; the future is with the soil, the endocrine glands."

It must be remembered that the dosage of products that are active as a result of their hormone content has quite a different basis from that of drugs: There is no definite dosage, save "dose enough." Joseph Pratt, of Boston, has said: "As all internal secretions are stimulatory substances and do not furnish nutritive material to the cells, they are able to exert their specific action when present in very small quantities."

To one who uses the hormone-bearing extracts for any length of time, and who thus has an opportunity to appreciate their specificity and value, the subject assumes a most important aspect, since it makes possible results otherwise unattainable. In the words of Leonard Williams, this is "a subject of inquiry as fascinating as any in the whole range of medicine, and as fruitful in promise as any in the whole range of therapeutics."

SECTION II. CHAPTER 3

FAILURES WITH ORGANOTHERAPY

As with every phase of the treatment of disease we expect to encounter a certain proportion of failures with the administration of organotherapeutic preparations. It could hardly be otherwise, for we have not found the long-sought "Elixir Vitae" which Ponce de Leon and others have vainly looked for.

If we are wise, our failures will become our greatest assets, for through them we may learn more than in any other way. A graduate from the "University of Hard Knocks" always is a better-posted and more dependable man than the one who has secured most of his information easily by avoiding the failures of others, though, naturally, our course in this "university" can be shortened materially by being awake to what others are doing.

During my experience I have often heard statements something like this: "I tried that treatment faithfully for several weeks, and it seemed to do no more good than other things we used before. I'm afraid I haven't much use for ....."—corpus luteum, mammary extract, or even thyroid gland have been mentioned. At times organotherapy as a whole has thus been criti-

cised, despite the apparent limitations of the speaker's clinical testing.

This profitably may be used as the text for a short "sermon" which may develop some helpful suggestions for those who are expecting great things from organotherapy, and to whom it may be a somewhat new procedure.

First of all we must admit that usually organotherapy has been tried in difficult cases of long standing where other measures have been tried, perhaps repeatedly and by many physicians, and have failed. Here, naturally, the results will be less satisfactory just as any treatment is likely to be less effective the further advanced and more complex is the disease. It is true that organotherapy deserves consideration in just this class of cases, for it has been remarked many times that when other things have failed, organotherapy has enabled us to get wonderful results, and, perhaps, we may have acquired an undue enthusiasm, and expect too much of this method. None the less we must not deprecate organotherapy for this reason merely because we can not use it to accomplish the impossible.

There is another very important factor that sometimes seems purposely to be ignored, especially by those who don't want to be convinced! We have seen that the real basis for the benefits to be expected from organotherapy lies in the principle of homostimulation. This means that we must have active preparations and responsive organisms. It is possible to have an inactive remedy, I will admit, though in these days such products far excel those of years ago; but how about the reactivity of the patient and the response of those cell-aggregates that it is desired to arouse or set into renewed motion? Especially in chronic disease where the conditions are the results of constant and long-continued irritation, malnutrition or toxemia, the re-education of the worn-out endocrine organs is no small task. And, too, the degree to which the endocrine glands are affected in one case as compared with another seemingly quite similar, varies very much indeed. Again, there is a very decided though intangible personal element, for one individual responds to hormone stimuli rapidly and thoroughly, while another does not. One child "catches everything going," while another "has never been sick in her life." It is merely a matter of the physiological substratum—and this indeed is an indefinite quantity.

Nevertheless we will continue to use organotherapy expecting a certain percentage of delayed results and even some entire failures, and are more than satisfied with the numerous excellent responses to the natural hormone stimuli that the administration of glandular extracts makes possible.

Another cause of failure is due to stopping before one should. In our "text" above, "several weeks" is the time stated as being the limit of the doctor's patience. Now organotherapy is useful

largely because it is a means of educating certain organs to perform their service to the body as a whole. Education is not a matter of days or even weeks. It takes many years to educate the mind. The gastro-enterologist knows that it takes months to educate the liver, gastric cells or other organs to perform the task which through various circumstances has been given up or done unsatisfactorily. When we give morphia we expect practically immediate results. It works quick, not by "education" but by paralyzing certain functions. Strychnia also works quick, not by "education" but by abnormal stimulation, and how long do such effects last?

As a matter of fact the subtle influence of hormone therapy is indeed a re-education of certain organs, and this always takes time and, as we have seen before, depends a great deal upon the responsiveness of the cells. To be successful organotherapy should be added to other treatment, drug, hygienic or dietetic, and should be continued always for a generous time; and further, it should be "tapered off" to see how well the endocrine glands can get along without these additional stimuli.

Still another potent cause of failure is the not unusual tendency to ignore the intimacy of the ductless glands and their most important interrelations. The subject of reinforcing this extract or that is given comprehensive consideration elsewhere; and I merely mention as one of the causes of failure, a habit of overlooking associated derangement of other glands which are dependent upon or at least associated with, the particular ductless gland which may have been discovered to be at fault and which is being treated with organotherapy. In other words, combining gland extracts is likely to make for better results, and here, let me say with emphasis, is the "open sesame" to the successful application of organotherapy in a generous percentage of all cases in which this measure is indicated. It is not possible for a single endocrine organ to be affected, slightly or seriously, without reflex (hormonic) effects upon others of the allied organs.

There has been a good deal of comment, especially in some manufacturers' literature, about the organotherapeutic treatment of certain organic diseases, especially of the central nervous system. These statements have led some to expect "cures" in such diseases as locomotor ataxia, multiple sclerosis, paralysis and other diseases generally conceded to be "incurable." I do not deny that increased endocrine function is helpful in an organism afflicted with such diseases as those mentioned just as in any others, but it does not replace the destroyed nerve cells, and can not. Organotherapy may be indeed helpful in such hopeless cases, but it is far from curative and it should be obvious that if this method really cured locomotor ataxia, the manufacturers and their fortunate medical customers would never lack

either opportunities to serve or the financial rewards which would naturally come with such a service. Organic disease is not amenable to organotherapy in the degree that we expect functional disease to respond to it—it simply can not be so.

Finally, quite the most important of all the causes of failure with organotherapy (and, for that matter, any other method of treatment) is *an incomplete diagnosis.* Too often we learn what is the matter with our patient, but not *all* that is wrong. I have repeatedly stated that the medical profession commits more sins of omission than of commission. We overlook things. Why, the minor form of hypothyroidism is more than commonly ignored entirely! The consideration of the endocrine side of disease has been passed by until very recently. Disorders of the ductless glands had to be "real diseases" before we recognized them, and hidden functional aberrations were never sought for. Now all is being changed and as our eyes are being opened to the importance of *functional pathology* not only are we recognizing the early influence of endocrine dysfunction, but we are learning to consider our patient as a whole rather than as an individual with some obvious disease.

Here, then, lies the greatest source of failure in medicine—we have been treating diseases rather than patients! So long as we consider a case of, say hypothyroidism as being suited for organotherapy and ignore the demineralization (see Sec. V, Chap. 16), the acidosis or hypoalkalinity or the original active cause of the disturbance, some hidden focal infection, a dilated and overloaded colon, a dietetic habit (such as coffee-drinking) which has overburdened the detoxicating department of the body or other common underlying causes of disease, we are not going to get the optimal results from our organotherapy.

The reverse is equally true—even if we are most thorough in our diagnosis, and our clinical and laboratory findings are about perfect, we can reduce the efficacy of our treatment quite considerably by omitting to consider the effect that the various derangements may have had upon the endocrine functions and with this information in mind, make a concerted effort to encourage these overworked glands and favor the re-establishment of their normal functional service to the body—always in conjunction with the other obvious therapeutic measures that need to be applied in a given case.

There are other causes of failure with organotherapy which will occur to the thinking physician and which need not be mentioned here. For instance, if one is convinced that a certain procedure is destined to fail, likely as not it will! If the patient is sure your measures are not going to help, the psychic condition may indeed overbalance a large part of the possible benefit. So with organotherapy. We must realize that it is but a factor in our work and that we can not and must not expect the adminis-

tration of a few tablets or capsules to re-educate, rejuvenate and remake our patients.

SECTION II. CHAPTER 4

"THE PLURIGLANDULAR THEORY"

A fundamental principle which has broadened organotherapy in a very decided manner is embodied in the following statement: "Pluriglandular disorder is much more frequent than disorders involving a single gland of internal secretion; hence the reinforcement of an indicated organotherapeutic extract with one or more synergists many times radically alters the results for the better. In fact it may make the difference between success and failure."

It is not difficult to understand that a general influence for harm, toxic, nutritional or emotional, hardly can be expected to limit its effects to a single small part of the organism. A severe toxemia such as we find in pneumonia, typhoid fever, intestinal stasis or poisoning with alcohol, morphine or other drugs, deranges the function of the body as a whole although in one instance a certain part of it, say the liver, may be more obviously disordered than another. This applies equally to the endocrine glands and the writer frequently has said with emphasis that "there never was a uniglandular endocrine disorder!" This may seem to be a rather inclusive statement; but it would be difficult to convince me of the reverse, for once one has learned the principles underlying hormone action and the extreme intimacy of the endocrine glands as well as their close dependence the one upon the other, it is not easy to conceive of any obvious or hidden disease process affecting only one or two of these remarkable little organs to the exclusion of the others. They may be remotely situated from one another, but they are very closely bound together by hormone ties.

Clinical Endocrine Relationships. The subject is so important and the clinical and therapeutic deductions are so valuable that it may be well to give some more attention to this "theory." Take as an example a fairly common ductless glandular disorder—hypothyroidism. It is seen in all gradations and its own direct manifestations are always intertwined with those of other origin. No case of myxedema or cretinism, or even of the less marked but more important minor forms of thyroid insufficiency, shows the manifestations of thyroid dysfunction alone. Metabolism as a whole is reduced—and the thyroid is not the only endocrine gland concerned in the regulation of metabolism. Gonad function is disturbed, and in cretins it practically

never develops at all. Thyroid disorder is so very commonly associated with menstrual functions that the gynecologist should never consider a case of menstrual derangement without also considering the thyroid function with that of the ovaries. The sympathetic system, which we have every reason to believe is controlled by the hormones produced in the chromaffin tissue of the adrenal glands, is very decidedly affected in hypothyroidism, and in the well marked cases the blood pressure is low, circulation is very much below par, and the usual sympathetic reactions are dulled or even lost.

Again the so-called "compensatory hypertrophy" of some glands during functional or organic insufficiency of some other intimately associated gland of internal secretion adds to the impression that these organs must be considered together rather than separately. The cycle of the development and atrophy of the mammary glands in relation to the variations of ovarian function is one instance; the not infrequent enlargement of the thyroid (and more rarely the pituitary) during the period of normal ovarian inactivity—during gestation and at the beginning of the menopause; possibly the interstitial glandular hypertrophy of the prostate when the testes are in process of normal atrophy; and other physiological functional dependencies which we do not need to mention, all tend to the conviction that we must no longer consider endocrine disease, functional or organic, as involving the gland or glands alone which most obviously are affected.

Synergistic Organotherapy. This being the case we should be able to make good use of this principle in our work, both diagnostic and organotherapeutic; and the added information that we acquire by viewing various symptoms-complex from the "pluriglandular viewpoint" are just as encouraging as the better results that we get from pluriglandular as compared with uniglandular endocrine preparations.

In brief, then, the facts warrant the combination of synergistic gland extracts no matter whether we can see clear clinical evidence of disorder of these synergistic glands. It must be remembered that symptoms do not necessarily manifest themselves for quite some time after the beginnings of actual dysfunction in the cells. The ovarian side of goiter, or the thyroid side of dysovarism does not always accompany the first evidences of disturbed secretion in the gland originally affected.

Nor must we limit our new viewpoint to pairs of organs like the thyroid and the gonads just referred to. In hyperthyroidism, for example, not only may we find deranged ovarian function, but I am confident that not a few of the symptoms of sympathetic irritability are not so much due to the excess of thyroid stuff itself as to the undue stimulation by it of the adrenal glands. Really then what we call hyperthyroidism often is hyperadrenia! Or hypercrinism—a generally increased endocrine activity due

to a condition which has increased thyroid secretion beyond all reasonable bounds and consequently simultaneously has stimulated the pituitary, adrenals, gonads and other endocrine glands. If this is the case, medication to be successful should take the whole endocrine system into consideration and not the offending thyroid alone. The same applies even more to conditions of hypocrinism which result from pluriglandular insufficiency.

Combinations Superior to Single Extracts. This explains why combinations of various endocrine preparations so often excel single extracts. In previous communications, and in both of my books referred to elsewhere, I have strongly urged the combination of suited products of this kind. The profession is thoroughly converted to moderate polypharmacy, and we combine our A. B. & S., or our I. Q. & S., our mercury and potassium iodide, or many other well-known pharmaceutical products. Rarely is a prescription written for a single remedy, for we are absolutely convinced that synergism is possible in pharmacology just as it is in physiology. Should there, then, be any real basis for criticism of pluriglandular therapy by those who routinely apply the same principles in polypharmacy, especially when we recall that the blood itself contains in solution a host of differing chemical substances, some synergistic and some antagonistic?

As a matter of fact such portions of a pluriglandular mixture given per os as are absorbed into the blood, merely amplify the sum total of hormones circulating in the blood and according to the principle of homostimulation already outlined, arouse into increased functional action those organs whose work it is to produce hormones similar to those which have been administered. Thus hypocrinism is reduced and the aggregate of hormone stimuli is increased.

SECTION II. CHAPTER 5
A HYPOTHESIS OF "HORMONE HUNGER"

Certain fundamentals in medicine as in other sciences necessarily must be based upon hypotheses, for it is not accorded to man to know all of the Creator's work. We are confident that scarlet fever, measles and even "flu" are of bacterial origin; but we have yet to isolate and identify the offending organisms, as we have done, for instance, with the typhoid bacillus. Again the "accepted explanation" of the processes of immunity is the "side chain theory" propounded by Ehrlich; and today this hypothesis is as far as we can go in giving a reason for the "immunizing response" of the body and the "how" of its remarkable and

almost automatic resistance to invasion of any part of the body by disease-producing microorganisms.

The clinician has to presume many times. Facts are not always so easy to secure. On the other hand, the physiologist hesitates to presume—he must be scientific and empiricism has no place with him. Despite this it happens that neither clinician nor physiologist really understands how the hormones of the glands of internal secretion are made and used. We have satisfactorily proved their existence and that many of them are definite chemical entities, some of which already have been isolated in crystalline form. We are certain that they are secreted into the blood or body fluids and thus carried to distant organs or cells to "correlate the activities of the organ of origin with the remote but associated organ that it influences."

How these hormones are carried, whether they are produced in the same form that they are used* and exactly how they reach the cells which they are destined to "arouse, or set in motion," is not now definitely known. We must theorize—a hypothesis is in order.

For a number of years I have been studying this subject and not a few clinical experiences with various forms of organotherapy in certain endocrine disturbances have convinced me that there are varying degrees of receptiveness to hormone stimuli on the part of various individuals. In other words, where in one instance a very rapid and remarkable result may be secured, in another seemingly similar case the reactivity of the patient differs and the results are not so good or so rapid. This has caused me to ponder on the subject and I have evolved what I have chosen to call "a hypothesis of hormone hunger" which I will attempt to explain.

Selecting the Hormones from the Blood. Each organ of the body that is dependent upon hormone influences must have some subtle capacity to pick up the hormones from the blood as they float by. This cannot but be true, else how could the passing "chemical messengers" bring about the influence upon the organ or cell that they are supposed to affect? Not only must there be a definite capacity to pick up these hormones as they are brought to the cell by the blood, but there must be a selective capacity, for the blood contains all the hormones that we know of as well as probably a good many more that we do not know at present. I do not feel that the imagination has to be stretched very much to presume that there is a remarkable "cellular judgment" or

* In 1913 I had the opportunity of doing some interesting work with Hustin in the Institut Parc Leopold, Brussels. He showed that secretin activated the secretory cells of a pancreas separated from the body—in a paraffin bath; but the most active secretin solution *had to be mixed with blood* before it would do the work.

selective capacity to pick out the hormones that are needed—*and in the amount that they are needed.*

It is with this particular selective power in mind that I have developed this hypothesis of hormone hunger. I contend that under varying circumstances these cells must be more active in their picking up of the passing hormones than at other times. In other words, at times a condition of hormone hunger actually must be present. Let me explain: Take as an example the thyro-ovarian interrelationship—this is, perhaps, the most thoroughly established and most easily understood. It is well known that there is a principle produced in the thyroid gland which exerts a very marked influence upon ovarian function. (It will be recalled that in myxedema there are definite functional ovarian disorders, that girls with goiter very often have serious menstrual difficulties and, finally, that the cretin, who has no thyroid gland, does not develop sexually.) Surely it is fair to believe that there is a principle made in the thyroid which stimulates ovarian function, and that this must necessarily reach the ovaries through the blood, and, of course, that the ovaries must have some means of getting hold of this hormone. If, then, this thyroid hormone passing through the ovaries in its blood supply happens to be deficient, after as much of it as can be found is taken up by the cells of the ovary, and the demand is greater than the supply, there will remain a need for that which is not present, i. e., the ovarian cells will be "hungry" for more of the thyroid stimulus. Further this "hunger" will vary, depending upon the degree to which the thyroid is functioning and the ovarian needs.

A Case in Point. In a case with well defined hypothyroidism it is reasonable to suppose that the ovarian cells are getting along as best they can with little or none of their usual stimuli (and right here enters the fascinating study of the effects of hormone hunger upon other endocrine glands—how the pituitary, for instance, may function faster to make up for deficiencies in its associates, etc.). If we attempt to modify the clinical disturbances which result from this hormone insufficiency by means of organotherapy, the application of this hypothesis enables us to appreciate that the "hormone hunger" of these ovarian cells increases their presumed "urge" to pick out from the circulation such additional hormones as we may be able to give by mouth (and incidentally to benefit from the enhanced hormone production which follows organotherapy, upon the principle of "homostimulation" as outlined in Hallion's law*) and to under-

* The "law" propounded by Hallion (*Presse Medicale*, 1912, XX, 433), explains the principle named "homostimulation." It is as follows: "Extracts of an organ exert on the same organ an exciting influence which lasts for a longer or shorter time. When the organ is insufficient, it is conceivable that this influence augments its action, and, when it is injured, that it favors its restoration." (Translation made in my book "Practical Hormone Therapy," p. 24.)

stand that this particular phase of the hormone-influenced organ's selective capacity will be the greater in direct proportion to its individual cellular need for such substances.

To put this in another way: If we give thyroid extract as a therapeutic measure in dysovarism, the ovaries are unusually interested in securing the thyroid hormone which may get into the blood, and they will select it with greater avidity, depending upon the degree of "hormone hunger" that may be present; and as soon as the necessities of these glands have been satisfied, the unusual facility with which the hormones are picked out from the blood stream will cease, and we presume that superfluous amounts of any or all of the hormones will remain in the blood either until they are used later on by any organs that may be able to avail themselves of their stimuli, or are finally oxidized in the usual manner.

There is another phase of this matter which appears to me to be of importance, and which I think is more satisfactorily explained by this hypothesis than in any other way: We are convinced that the intimate interrelationships of the glands of internal secretion practically eliminate the possibility of endocrine disturbances involving a single endocrine gland. That is to say, when there is a disturbance of one internal secretory organ, immediately there develops an associated functional derangement of the hormone balance, involving one or more of the glands most intimately dependent upon the originally affected gland. Hence pluriglandular disturbances are the rule, and, therefore, pluriglandular therapy must take the place of the old-fashioned administration of the most obviously needed glandular extract. As yet this position is not generally accepted, and some members of the profession still assert that this is "shot-gun therapeutics." Others, whose clinical experience and view-point is broader, now insist that in the combining of various related glandular products we are finding much greater clinical satisfaction—and the "crucible of the clinic" as George W. Crile calls it, is the only real test of any new or modified therapeutic measure. In passing, take as an instance the cretin, who it is well known is in dire need of the physiological stimulation resulting from the thyroid hormones. Many times a cretin develops remarkably on thyroid alone, and then reaching a seeming barrier beyond which no progress is made. If, then, the associated glands, especially the anterior pituitary is given *with the thyroid,* the progress is reestablished and sometimes far excels that previously made. This also applies with equal force in many other pluriglandular dystrophies, the most common of which is the thyro-ovarian dysfunction already mentioned.

An Explanation of Pluriglandular Therapy. This brings me to my final point: This hypothesis of hormone hunger explains the "how" of pluriglandular therapy. Many times I have

wished that it were possible to determine the degree of glandular insufficiency in a given individual, just as we can estimate the urinary solids and differentiate the percentage of urea, chlorides, phosphates, etc., in figures, or as we do in the differential blood count. It would be ideal to be able to establish that, for example, a given case is 50% low on thyroid, 75% low on ovarian, and 20% low on pituitary hormone functioning. Obviously this would facilitate a definite therapeutic recommendation; but we cannot do this, although my Thyroid Function Test (see *N. Y. Medical Record,* August 3, 1918) is quite a step in this direction in the study of one of these dyscrinisms. How, then, can we treat these cases scientifically? We cannot; but by depending upon the hypothetical principle of "hormone hunger" just enunciated we can offer a pluriglandular mixture *and allow the body to do its own selecting.* We can trust the organism to pick out from the menu we offer it those hormones that it needs most and, too, in the degree that it needs them. Then, based upon the previously mentioned condition which might be called "hormone satiety," the limited excess of unused hormones floats on until used up or destroyed. This explains to me the reason for the clinical experience many of us may have had with the same pluriglandular therapy in several somewhat dissimilar cases: In one case a thyroid influence predominates, in another a pituitary and the third an ovarian, all because in these three instances the hormone hunger made it possible to grab the various respective hormones with a greater avidity and rapidity.

Whether this hypothesis is as well founded as the Ehrlich "side chain theory" of immunity, is not for me to say. It explains many things that I have seen repeatedly in clinical organotherapy and I believe it is based on sound reasoning and worthy of consideration. At all events this remarkable selective capacity of the hormone-influenced organs or cells is something that cannot be gainsaid; and the clinical results are certain enough whether the hypothesis is well-grounded or not.

SECTION II. CHAPTER 6

A CLASSIFICATION OF GLAND EXTRACTS

Obviously not all of the extracts obtained from various organs can be expected to be of equal therapeutic merit, nor are they used and recommended with equal frequency; hence, it seems advisable arbitrarily to separate these preparations into several classes:

(A) Those which are of well-known and practically unquestioned therapeutic efficacy;

(B) Those which are not so well known, but which, nevertheless, offer undoubted possibilities in medicine; and

(C) Those which have been used slightly, which are occasionally referred to in medical literature, but as yet have a comparatively limited usage.

With the above in mind, this classification will be made as follows:

Class A. The Better Known Organotherapeutic Remedies

1. Adrenals—I. Medulla
2. Bile
3. Duodenum (Secretin)
4. Mammae
5. Ovaries (Corpus Luteum)
6. Pancreas—I. Pancreatin
7. Pancreas—II. Trypsin
8. Pituitary—I. Posterior Lobe
9. Stomach—I. Pepsin
10. Thyroid

Class B. Less Well Known but Useful Products

11. Adrenals—II. Total Gland
12. Adrenals—II. Cortex
13. Blood—I. Hemoglobin
14. Blood—II. Normal Serum (Coagulose)
15. Blood—III. Antithyroid Serum
16. Blood—IV. Leucocyte Extract
17. Bone Medulla
18. Brain (and Spinal Cord)—I. Lecithin
19. Brain—II. Thromboplastin (Kephalin)
20. Kidneys
21. Liver
22. Lymphatic Glands
23. Pancreas—III. Total Gland
24. Pancreas—IV. Langerhans Islets
25. Parathyroids
26. Placenta
27. Pituitary Body—II. Total Gland
28. Pituitary Body—III. Anterior Lobe
29. Prostate
30. Spleen—I. Total Gland
31. Spleen—II. Peristaltic Hormone
32. Testes (Orchic)
33. Thymus—I. Total Gland
34. Thymus—II. Nuclein (Nucleinic Acid)

Class C. Extracts Used Infrequently

35. Appendix Vermiformis
36. Bone
37. Brain and Cord—III. Total Substance
38. Lung
39. Parotid
40. Pineal Body
41. Stomach—II. Gastrin
42. Tonsils

Of course it should be understood that this is quite an arbitrary classification, made merely as means of noting at a glance the writer's idea of the comparative therapeutic availability of an extract.

In the pages which follow the reader will be able to distinguish quickly the class to which any given preparation belongs. It may be added that the following outlines comprise the majority of the indications and suggestions found in current medical literature; and for further convenience the less well-known indications have been separated from the principal ones.

SECTION III

PRACTICAL ORGANOTHERAPY

In 1918 I published two small books—"Outlines of Organotherapy," *which was an effort to condense the essential facts concerning gland feeding into a small, concise* vade mecum, *and a brochure called* "Pluriglandular Therapy." *The former was quite a success and the original edition was speedily exhausted. Instead of reprinting it in the same form and under the same name, its contents, still further boiled-down but amplified, constitute the first part of this section. The second booklet went through three large editions of 15 months. The material for this booklet, very considerably enlarged by the addition of much information concerning special formulas that have been worked out for various physicians, forms the second part of this section and it, in turn, has been subdivided into two parts for obvious convenience.*

The first half of this section is indirect and general in its application, while the second refers to definite pluriglandular preparations made following my own studies (and those of many friends) in my own laboratory. Each part is important, the last probably more practically so.

SECTION III. PART 1

OUTLINES OF ORGANOTHERAPY

CLASS A:—THE BETTER KNOWN ORGANOTHERAPEUTIC REMEDIES

1. THE ADRENAL GLANDS—THE MEDULLA

Source and Form. The suprarenal capsules of various animals, chiefly cattle. Available in powder; but generally used as the active principle, adrenalin, isolated by Takamine in 1901, and obtainable as a crystalline powder or, most commonly, in the form of a 1:1000 solution of the chloride. (Synthetic preparations of identical or closely allied chemical composition are now made.)

Physiologic Relations and Action. The adrenal medulla, concerned with the control of the sympathetic system, exercises an essentially vascular function, in contradistinction to the antitoxic function of the cortex. Acute adrenal insufficiencies frequently supervene in severe infectious diseases. Pain (as well as other emotions, i. e., fear, rage, etc.) causes an increased elimination of the adrenal principle (adrenin), and after adrenal exhaustion, muscular asthenia and vascular atonicity supervene. Adrenalin in extremely small doses, contracts the blood vessels when applied locally or given internally, by acting upon their nerve terminals. It also stimulates to contraction many groups of unstriated muscle (uterine muscle is a notable exception) and exerts a particular influence upon cardiac muscle, increasing its tone. This, with the constricting action on the vessels, causes the rise in blood pressure which follows its increased production or its administration.

Principal Therapeutic Indications. Necessarily divided under two headings: (1) *Its local effect*—vasoconstriction in conditions of congestion or local hemorrhage, as in: Conjunctivitis, coryza, eczema, epistaxis, hay fever, hematemesis, hematuria, hemorrhoids, iritis, keratitis, laryngitis, pruritus, rhinitis, tonsillitis, urethritis and as a vaso-constrictor during local operations, etc. (2) *Its general effect*—controlling conditions due to disturbed vasomotor equilibrium and to hypoadrenia, where the work of the chromaffin tissue (adrenal medulla) seems to have been more especially affected. Among these are: Asthma and bronchial spasm, Addison's disease, cholera, collapse and shock during severe infectious diseases and from other causes, dysentery, Graves's disease, heart failure, osteomalacia, etc.

Other Minor Indications. Adrenalin has been recommended in snake bite (locally and internally) and other poisoning, especially by strychnine; and similarly to prevent the "nitroid crises" which occasionally accompany arsphenamine (salvarsan) injections. Also used in certain vascular dermatoses as herpetic purpura, angioneurotic edema and urticaria. Recently it has been used successfully in Bright's disease, especially in children.

Contraindications. All save the slightest degrees of hemoptysis; extreme hypertension; diabetes mellitus and pancreatic insufficiency.

Synergists. In local surgery adrenalin is commonly used with cocaine, procaine, etc.; in asthma it has been recommended (Zueblin) with Liq. Hypophysis.

Administration and Dosage. Adrenalin medullary substance in powder or tablets, 1-10th to ¼th of a grain every hour or, in certain cases, 1 to 2 grains three times a day in chronic conditions. Adrenalin (or similar products), 2 to 10 or occasionally even 15 minims of a 1:1000 solution by mouth, hypo-

dermically, or, in extreme cases, by intravenous injection well diluted with saline solution. Adrenalin solution is recommended to be used as follows: For hypodermic use, 5 to 15 or more minims of a 1:2000 solution injected into the muscles. For intravenous use, 1 or 2 mils. of a 1:5000 solution. For local use a solution of 1:1000, 1:10,000 or even 1:100,000 may be used.

Remarks. Generally speaking, the use of the adrenal principle is limited to its local application in minor surgery and for the vasoconstrictor action. The systemic influence is equally important and the use of adrenalin or, better still, desiccated adrenal substance in acute functional adrenal insufficiency is of marked value. In acute cases the active principle is used and in chronic cases total adrenal substance is preferable.

2. BILE

Source and Form. The bile of cattle or, preferably, hogs. Usually available in the fresh state, inspissated (Extractum Fel Bovis) or desiccated (Powd. Bile Salts), the second in the form of pills and the last in powder or enteric-coated tablets. The bile salts are now isolated.

One part of dehydrated bile represents about 30 or 40 parts by weight of the fresh fluid. Extractum Fel Bovis is a heavy, syrupy liquid 1 part representing 8 parts of ox-gall.

Physiologic Relations and Action. Bile is the most effective, physiologic cholagogue. It is a direct antagonist to intestinal putrefaction and also exerts a specific anticoagulative action upon the mucin in the intestines. It is said to have a slight stimulative action upon the intestinal musculature and to augment the activity of the pancreatic and duodenal enzymes.

Principal Therapeutic Indications. Hepatic and biliary insufficiency and stasis with indigestion, constipation and alimentary autotoxemia; cholecystitis and cholangitis; biliary calculi with or without colic; catarrhal jaundice; muco-membranous entero-colitis. In children with fat indigestion, foul stools and anemia.

Other Minor Indications. Used as an adjunct in the treatment of a number of nutritional conditions associated with hepatic insufficiency, among them tuberculosis, toxic neurasthenia, migraine, etc. Also recommended for hyperpepsia.

Contraindications. Obstructive jaundice.

Synergists. Hepatic substance (q. v.) fits in well with bile, broadening its value. Pancreatin is often used with it. These three remedies may be given together with good prospects of better results than those expected from the one alone.

Administration and Dosage. Two to 5 grains of the repurified, desiccated product, or 5 to 15 grains of the inspissated

ox-gall, taken with or immediately after food. In chronic cases one dose at bedtime is often sufficient, provided it is continued for some weeks or months. In chronic biliary stasis and gallstones it is advisable to continue the administration of bile for months; in acute cases 5 grains may be given every two hours.

Remarks. Considered by many French internists to be a virtual specific for mucous colitis or enteritis. In such cases it must be given in ample doses by mouth and may be supplemented by the bile enema (4 or more ounces of warm water in which one dram to one ounce of fresh ox-gall has been mixed), repeated each night a number of times.

3. THE DUODENUM (SECRETIN)

Source and Form. The upper eighteen inches of the small intestine of pigs, extracted by HCl from duodenal scrapings and obtainable in the form of powder or solution.

Physiologic Relations and Action. Secretin is the so-called "alimentary hormone" discovered by Starling which, he demonstrated, liberates and activates the digestive enzymes from the pancreas. It was later shown that secretin combines with the granules or proferments in the cells and actually forms a part of the completed ferment. Secretin also stimulates the production of bile and succus entericus and increases the capacity of the duodenal walls to produce more prosecretin.

Principal Therapeutic Indications. Indigestion with pancreatic insufficiency associated with clay stools, intestinal putrefaction, autotoxemia and indicanuria; functional indigestions generally including severe digestive disturbances of infants and children (summer diarrhea, marasmus, etc.); following gastroenterostomy and intestinal shortcircuiting. In cancer where the normal HCl is absent, and hence secretin production is either reduced or absent, secretin may be of value to enhance the digestion.

Other Minor Indications. Recommended in certain forms of diabetes, but aside from its action upon digestion, it has no advantage and this phase of its administration has been dropped.

Contraindications. Duodenal ulcer and pancreatitis. Occasionally it may slightly aggravate hyperchlorhydria.

Synergists. Pepsin, pancreatin and other products influencing digestive activity.

Administration and Dosage. Two to 5 grains of the repurified duodenal extract before meals. In the treatment of infants a portion of a tablet or cachet representing ¼ to ½ a grain should be given with each feeding.

4. THE MAMMARY GLANDS

Source and Form. The parenchyma of the udders of cows, goats or ewes. Available in powder or tablet form.

Physiologic Relations and Action. The internal secretion of the mammae antagonizes that of the ovary and is also antagonized by it; hence it serves to inhibit conditions resulting from hyperovarism. It stimulates mammary activity and development. It reduces congestion and oozing, and favors uterine involution after childbirth.

Principal Therapeutic Indications. Uterine diseases accompanied by hemorrhage, not due to organic causes (such as foreign bodies, cancer, etc.). Menorrhagia and metrorrhagia, with or without other menstrual disturbances. Interstitial metritis, including uterine fibroids. Deficient lactation, as an adjuvant to local measures in caked breast (to prevent stasis and increase the flow of milk). After parturition to hasten involution of the uterine walls.

Other Minor Indications. Conditions due to ovarian hyperactivity, such as nymphomania, as well as in ovarian and other diseases associated with much pelvic congestion and consequent pain. As a palliative antihemorrhagic in uterine cancer.

Contraindications. Deficient ovarian activity, including infantilism, amenorrhea, etc.

Synergists. Placental extract exerts a similar galactogenic and utero-depletant effect and may be given with mammary substance with advantage. Pituitary gland (total) also exerts a synergistic effect. Ergotin, cotarnine, etc., may be used to augment its styptic action. Recently thymus extract has been recommended.

Administration and Dosage. Two to 10 grains t. i. d., preferably with meals. In menorrhagia with or without fibroids continue for several months, the dose being increased during the flow and reduced during the intervals.

Remarks. One of the few organotherapeutic agents used to antagonize the results of excessive activity of another endocrine gland, and is an important representative of this class (so-called "antihormones"), and deserves to be used much more frequently in many conditions due to or associated with ovarian excess, and before more serious and radical measures are undertaken.

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5. THE OVARIES

Source and Form. Ovarian extract, i. e., extract of the whole ovary, for a time was practically supplanted by extracts of the corpus luteum of pregnancy obtained from cows or sows. Desiccated extracts of the total gland or of corpora lutea alone

are available in tablet, capsule or powder form. It is occasionally used by hypodermic injection.

Physiologic Relations and Action. The corpora lutea and ovarian stroma both produce remarkably active hormones which control menstruation and maintain pregnancy in the early months. They also regulate the oxidation processes. Suitable preparations of ovary or corpus luteum stimulate the ovaries and regulate the menses and those conditions dependent upon this phenomenon.

Principal Therapeutic Indications. (1) Organic ovarian deficiency: To replace the normal ovarian hormone action when the ovaries are destroyed by disease, removed by operation, inactive due to congenital maldevelopment or physiologically reduced by the menopause. Counteracts the nervous, mental and circulatory disturbances so commonly associated with such changes, and in infantilism, it favors development of the reproductive organs and the establishment of their activities. (2) Functional ovarian deficiencies: Menstrual disorders due to reduced ovarian activity caused either by local disease in or near the ovaries or from diminution of the stimuli normally received from the thyroid, pituitary, etc., including amenorrhea and certain forms of dysmenorrhea. Neuroses, especially the so-called "reflex neuroses" (including palpitation, dizziness, insomnia, depression, excitation and functional mental disturbances); nutritional disturbances associated with ovarian disease (obesity, anemia, certain forms of rheumatism, dermatoses, etc.); circulatory disturbances resulting from ovarian disorder including "flashes of heat," local congestion, cardiac irritability, irregular pulse, etc.

Other Minor Indications. Osteomalacia, Graves's disease, neurasthenia and epilepsy, especially that form which is associated with, and aggravated by, the menses. Sterility of functional origin, and repeated abortions not due to organic disease or mechanical factors. Hyperemesis in early pregnancy, in which case the solution of the luteal principle is given hypodermically.

Contraindications. Pregnancy. Conditions of ovarian hyperactivity, such as mental and nervous hyperexcitability (sexual); extreme pelvic congestion (though occasionally this form of treatment may be beneficial in such cases); nymphomania, etc.

Synergists. Thyroid extract may be given with ovary with advantage in practically every case (save hyperthyroidism). Pituitary gland (total) is also used with it.

Administration and Dosage. Two to 5 grains of total ovary or desiccated corpora lutea, increasing to fifteen or twenty grains t. i. d. after meals. In chronic conditions the medication should be begun immediately after the menstruation ceases, in

order to affect the succeeding period, increasing the dose several days before the period is due. Discontinue during the flow; and in many cases prolong the treatment for months, gradually reducing the length of time during which it is taken each month. The hypodermic solution of the corpus luteum principle is given in daily doses of 1 mil. equal to 3 grains of desiccated substance. Six or eight injections are said to be usually enough.

6. THE PANCREAS—PANCREATIN

Source and Form. The desiccated and extracted acinous portion of the pancreas of cattle or hogs. Usually secured in a standardized powder and dispensed in capsules (hygroscopic and deteriorates when damp).

Physiologic Relations and Action. The pancreas produces three well-known ferments—trypsin, steapsin and amylopsin, which are capable of splitting up for digestion, proteids, fats and carbohydrates respectively. Pancreatic digestion is carried on in the small intestine and is an important factor in stimulating hepatic activity, hence there is also a "reflex value" from the use of pancreatin in hepatobiliary insufficiency. Pancreatin is rendered temporarily inert by the gastric juice but undoubtedly it regains its activity in the alkaline medium in the small intestine.

Principal Therapeutic Indications. The original use for pancreatin was in the peptonization of milk for feeding infants and invalids. It is chiefly used in the disorders of digestion, to augment the work of a faulty or overworked pancreas. The individual ferments are easily obtainable, and so far as the ferment value is concerned are gradually superseding the total pancreatic extract which is used for another purpose.

Other Minor Indications. Pancreatin is frequently recommended in tuberculosis. Brieger finds that its "power to lower the anti-tryptic index" is of value in tuberculosis and cancer. Certain forms of infantilism with obvious pancreas insufficiency are benefited. (Bramwell.)

Synergists. Other digestive ferments, pepsin, bile salts, etc.

Administration and Dosage. Three to 10 grains is an average dose. It is best given one hour after meals and repeated one hour later.

Remarks. From a strictly chemical or pharmacological standpoint it may seem inadvisable to give pancreatin by mouth or to combine it with other ferments. The two authorities mentioned above, as well as many others, specifically advise its administration by mouth and Brieger recommends that "no attempt be made to protect pancreatin from the digestive fluids, merely

giving the powder on the end of a knife blade." (*Med. Record*, Feb. 1, 1913.)

7. THE PANCREAS—TRYPSIN

Source and Form. Same as pancreatin. Four times more active than Pancreatin U. S. P. Obtainable in powder or standard solutions of it.

Physiologic Action. Digests proteid material. Increases "the powers of resistance," especially against tuberculosis. (It is suggested that this may be due to augmented digesting powers of the individual leucocytes.)

Principal Therapeutic Indications. (1) Local: As a "diphtheria solvent"; in abscesses, ulcers and sinuses to clear out purulent, dead tissue; by direct injection into tubercular abscesses. (2) General: In tuberculosis, cancer and, of course, in digestive disorders with proteid putrefaction, to increase intestinal digestion and also to enhance the phagocytic powers of the leucocytes.

Administration and Dosage. (1) A 10 per cent. glycerine solution is generally used. It is first diluted and injected in increasing doses, commencing with 5 minims (plus a suitable amount of saline solution) and increasing to 20 minims or more. Trypsin solutions are used for topical application, a special "Lotio Pancreatis" (Fairchild) being recommended for this purpose. (2) One to 5 grains of the powdered trypsin, administered during or after meals.

8. THE PITUITARY BODY—POSTERIOR LOBE (Infundibulum)

Source and Form. The posterior lobe of the hypophysis cerebri of cattle. Desiccated extracts are available in powder or tablet form; but are not often used since extremely active, standardized solutions of the purified principle may be secured in ampules.

Physiologic Relations and Action. The posterior lobe of the pituitary is quite unlike the anterior lobe, for it does not have the same glandular structure or action. It may be removed with impunity, which is not the case with the anterior lobe. It contains an extremely active substance which exerts a stimulating influence upon unstriped muscle which is especially marked on the pregnant uterus. It also stimulates renal secretion and mammary activity, and seems to favor carbohydrate metabolism. It is one of the most remarkable of the organotherapeutic extracts and its physiologic action is evident in a widely varying range of clinical cases.

Principal Therapeutic Indications. The solution of the infundibular principle (named Liquor Hypophysis in the U. S. P.

IX) is used to hasten labor after the second stage has commenced. It facilitates expulsion and it is claimed that recourse to forceps is obviated in 80% of those cases where instruments ordinarily would have been used. When injected intramuscularly or hypodermically (preferably the former) in many cases, especially where asthenia is present, it causes a prolonged rise of blood pressure, at the same time strengthening the heart, hence it is most useful in shock, cardiac weakness and heart failure (including myocarditis) and other organic conditions associated with reduced blood pressure. The "heart value" of pituitary solution is important, especially in hyperthyroidism. It stimulates the musculature of the milk ducts in the mammae, and also it seems, the secretory activity in a lesser degree. It has been used in hypogalactia and as a preventive of this condition. It is a marked diuretic and is therefore used in uremia, anuria, dropsy, etc. Paradoxically, diabetes insipidus is most satisfactorily controlled by injections of this principle. Its influence on unstriped muscle includes the musculature of the whole intestinal canal, and it is administered with great success in meteorism, especially following laparotomy. It is said to be more immediately successful in fecal impaction and acute intestinal stoppage with or without paresis, than any other remedy.

Other Minor Indications. It favors uterine involution and is not infrequently used as a postpartum remedy to control hemorrhage and reduce subinvolution. Since it stimulates the mammary glands it is of prospective value in threatening mammary abscess. It has been used in bronchial asthma in conjunction with adrenalin. Recently recommended in enuresis in children, and evidently an important addition to the therapeutic possibilities of this condition.

Contraindications. It is particularly important not to give posterior pituitary solutions in the early stages of labor, since rupture of the uterus is quite possible. Obvious obstruction of any kind, such as dystocia (fetal or maternal), malposition, etc. Hypertension and severe nephritis has been mentioned as a possible deterrent to its use. When used for its effect upon the intestines perforation or rupture is not impossible under certain circumstances.

Synergists. Adrenalin, as already noted.

Administration and Dosage. One half to one mil. of a standardized 20% solution representing 0.20 grams of fresh posterior lobe, obtainable in ampules of ½ and 1 mil. of a standardized solution. Smaller doses more frequently repeated are recommended by some—2 to 5 minims.* Intramuscular injec-

* With this in mind it may be well to mention that *Liq. Hypophysis* (Harrower) is put up in 15 mil. vials protected with a rubber covering and withdrawn from the package as with stock vaccines.

tion is preferred to the subcutaneous method, and the intravenous route is commonly used but has no great advantage over the other method. When given by mouth 1 to 5 mils. may be used, but here it is usually given in powder or tablets containing ¼ to 1 grain, t. i. d., and continued for some time. (As much as 15 or 30 grains three times a day has been given with benefit.)

Remarks. Pituitary solutions have entirely superseded adrenalin in the control of shock and acute cardiac conditions, since its action is more satisfactory and persists for a much longer period. Morphine counteracts it; if opiates have been given previous to its administration, it is necessary to increase the dose of pituitary. A second dose of ½ or 1 mil. may be given during labor, 45 to 60 minutes after the first injection.

9. THE STOMACH—PEPSIN

Source and Form. The mucous membrane of the stomach of hogs. Pepsin is principally prepared in thin scales, and is rarely given alone in the dry form. It is more frequently administered with hydrochloric acid of suitable strength or in elixir or tablet form alone or with suitable adjuvant remedies.

Physiologic Action. Digests proteids in an acid medium.

Principal Therapeutic Indications. Dyspepsia, hypopepsia and conditions in which gastric digestion is defective; pyloric stenosis with retention; gastric dilatation with butyric fermentation, etc.

Other Minor Indications. Frequently used in vehicles in which various standard drugs are administered. Solutions of it (with HCl) are also recommended as a vulnerary.

Synergists. HCl, pancreatin, etc.

Administration and Dosage. Two to 5 grains before meals, preferably in 1 or more drams of a 0.2 per cent solution of hydrochloric acid.

Remarks. Pepsin is at best a makeshift and a number of reports indicate that as a result of its continued use, the stomach "becomes lazy." In my estimation the philosophy of its therapeutic value is not nearly so rational as that of secretin (see page 38). It is, however, a splendid remedy *to start* the treatment of foul gastric conditions.

Gastric juice obtained from live pigs or dogs is on the market and is used for precisely the same purpose as the more easily obtained pepsin-hydrochloric acid mixtures.

10. THE THYROID GLAND

Source and Form. The thyroid glands of young sheep and lambs. It seems best that these sheep should come from

flocks grazed near the sea. Various preparations of thyroid extract are officially known in the majority of the Pharmacopoeias. In the U. S. P. IX appears the following: "The thyroid glands of animals (in U. S. P. VIII, "sheep") which are used for food by man, freed from connective tissue and fat, dried and powdered, and containing not less than 0.17 per cent nor more than 0.23 per cent of iodine in thyroid combination." It is available in powder, tablets or capsules. One part of desiccated thyroid, U. S. P. VIII, represents approximately 5 parts of the fresh glands; the U. S. P. IX preparation is slightly different, one part of dried substance corresponding to about 5½ or 6 parts of fresh glands.

Physiologic Relations and Action. The thyroid is probably the most important of the ductless glands, as it is the most thoroughly studied. It is responsible for the establishment and maintenance of many of the metabolic activities of the body. It favors oxidation, controls growth both physical and mental and is very closely related to practically all of the other glands of internal secretion, particularly the gonads, adrenals, pituitary and thymus. The thyroid is one of the chief detoxicating agencies of the body and is also intimately concerned in the immunity-producing mechanism.

Principal Therapeutic Indications. (1) Major hypothyroidism: Organic conditions where there is congenital absence or pathological destruction of the thyroid gland, as in myxedema, cretinism, etc.; and certain conditions demonstrated to be due to a combination of endocrine conditions in which defective thyroid action is prominent, such as infantilism, mongolism, certain mental disorders and forms of insanity, obesity, anemia, etc. (2) Minor hypothyroidism: A very large class of metabolic disorders is included under this heading. Among them are many dermatoses, chief of which are pruritus, prurigo, ichthyosis, pityriasis rubra, scleroderma, psoriasis and even lupus. Various ovarian disorders are reflexly influenced by thyroid therapy and it is recommended in dysmenorrhea, amenorrhea, mastodynia, chlorosis and certain climacteric disturbances preferably with ovarian substance. Also suggested in hyperemesis gravidarum, uremic convulsions of pregnancy and puerperal eclampsia. In simple goiter without evidence of thyroidism (my Thyroid Function Test is of differential diagnostic service) thyroid extract may act as a specific. Recommended in certain phases and symptoms of insanity including hysteria, melancholia, dementia and other psychoses, particularly those associated with thyroid disease or the menopause. Among other numerous conditions in which it is frequently used with varying degrees of success are the several forms of rheumatism, arthritis, defective oxidation as in obesity, migraine and even arteriosclerosis. Also useful in vaso-

motor conditions chief among which are chilblains and Raynaud's disease.

Suboxidation usually calls for thyroid therapy. Malnutrition and reduced circulatory efficiency (hyposphyxia) with undue sensitiveness to cold, cold extremities, hypotension, etc., often benefit from thyroid and other synergistic gland extracts. In conditions of asthenia and senility, one may expect to encounter waning thyroid function, and thyroid will help very much. According to a famous New York specialist, in elderly persons ¼ or ½ grain of thyroid a day "helps to keep the arteries soft," presumably by enhancing metabolism and thus reducing the toxemia incident to the slowed chemical and hormonic functions of normal or premature old age.

Other Minor Indications. Used in a large number of conditions supposed to be in some way due to thyroid disorder. Among those not already mentioned are torticollis, Dupuytren's contracture, hemophilia, uterine fibroids, rickets, enuresis, nephritis and progressive muscular atrophy. The results are often astonishing despite the prospect and very often the empirical use of thyroid has accomplished more than the most careful and scientific treatment.

Under the heading "Unclassified Uses of Thyroid" several unusual uses for thyroid are enumerated in "The Handbook of Therapy" *:

"Thyroid has been used with success in some instances of hemophilia and purpura hemorrhagica, as well as in the irregular hemorrhages of the menopause. It has been used in chronic rheumatism, especially where the attacks showed a general disturbance of metabolism, such as at one time an asthmatic attack, at another an indigestion attack, and at another a typical gouty joint attack. Small doses given for a considerable time are often successful in this kind of metabolic disturbance.

"Sometimes thyroid acts as a diuretic, and it certainly is an antidote to nitrogenous poisoning in insufficient kidney action Even uremic convulsions are sometimes kept in abeyance by the administration of thyroid. During a uremic attack the dose of thyroid should be large, as 10 grains of the dried extract three times a day. Such treatment sometimes apparently prevents convulsions and in some instances seems to aid in saving life.

"If not otherwise contraindicated, whenever there is excessive connective tissue development in any organ—in other words, a sclerosis or cirrhosis—a small dose of thyroid daily is of benefit. The dose should be so small that it could not cause evident signs of its physiologic activity. In many of these instances

* This excellent text book, published by the American Medical Association, is noted for its conservatism so it seemed advisable to make the quotation verbatim.

small doses of iodid, given daily for long periods, may be of as much benefit.

"Some clinicians have certified to, and even proved, in certain instances, the value of thyroid in inhibiting or causing resorption of carcinomatous growth. This is especially true of uterine carcinoma. The majority of investigators, however, have not found this treatment successful."

Contraindications. Hyperthyroidism and Graves's disease, rapid heart, palpitation and breathlessness.

Synergists. Very small doses of iodine, or iodides, frequently enhance the activity of thyroid extract, especially in simple goiter. Nucleinic acid.

Thyroid is "the great organotherapeutic synergist," small doses frequently adding much to the therapeutic values of many other glandular extracts.

Administration and Dosage. Very variable, but generally much less than is usually recommended (in a recent U. S. Pharmacopoeia the dose was stated as 5 to 10 grains). The French method of giving 0.1 gm. a day in divided doses is excellent. One-tenth to one-fourth of a grain very frequently is enough in conditions of minor hypothyroidism, while there is no definite dosage for the disorders resulting from an inactive or absent thyroid. Sometimes in such cases 1 grain three times a day will suffice, at other times, even in children, 10 or more grains a day can be easily tolerated. The dosage for each patient must be adjusted to the individual idiosyncrasies.

A word of warning should be given here about thyroid dosage. A well-known brand of thyroid tabloids is dosed on a basis of *fresh* gland substance, i. e., the content is really less than those of other makes for five parts of fresh substance is equal to one of the finished powder. There is danger in overlooking this for an inadvertent change from tabloids to tablets may multiply the dose by five.

Remarks. The evidences of over-dosage (thyroidism) are irritability both nervous and cardiac, tachycardia, insomnia with headache, slight tremor of the fingers, prostration and pains in the back and limbs. Such indications call for a removal of all thyroid extract and after, say, a week or less, the re-establishment of the medication in much smaller dosages. The proper dosage is sometimes only reached gradually. Frequently as much as 1 to 3 grains may be given to susceptible persons in a single dose just before bedtime. It is extremely important to avoid the indiscriminate use of thyroid extract (as, for example, in obesity) and it should only be taken under the most careful medical supervision.

CLASS B:—LESS WELL KNOWN BUT USEFUL PREPARATIONS

11. THE ADRENAL GLANDS—TOTAL SUBSTANCE

Source and Form. The suprarenal capsules of various animals, chiefly of cattle. Available in powder or tablet form.

Physiologic Relations and Action. The adrenal glands through their hormones maintain the tonicity of the involuntary muscles including those of the circulatory system, hence cardiovascular tone and blood pressure is largely dependent upon adrenal activity. Adrenal disease (first described by Addison and named after him) is invariably accompanied by severe asthenia, great muscular weakness and circulatory inefficiency. These same manifestations in lesser degree may result from functional adrenal insufficiency, a very common condition, since the adrenals have been shown to be stimulated by emotional strain (pain, fear, rage, worry, etc.), by abnormal endocrine function elsewhere in the body (especially hyperthyroidism) and by toxemia. There is a more or less well-marked adrenal phase to every infection and infectious disease. The outcome of severe and heavily toxic diseases, as pneumonia, cholera, etc., is a condition of acute adrenal depletion which might properly be called "acute Addison's disease." This differs from the Addisonian syndrome only in the degree and persistence of the symptoms, and the fact that in the latter there is permanent destruction of the adrenal structure.

Without a doubt the adrenals are concerned in all long-standing chronic infections, and tuberculosis is a typical example of this. Here again we find the adrenal trinity—asthenia, hypotension and malnutrition.

Principal Therapeutic Indications. Asthenia, easy fatigue, muscular atony (myasthenia) and all conditions of a "run-down" nature; cardiac insufficiency with circulatory stasis, hypotension, cold extremities or the so-called syndrome of "hyposphyxia"; malnutrition, especially accompanying or following conditions which obviously are due to or associated with hypoadrenia.

Addison's disease is temporarily amenable to adrenal gland feeding, and the symptoms already enumerated are often very satisfactorily controlled in this way. The actual progress of the disease is not stayed. The symptoms of Graves's disease may be reduced very materially by adrenal feeding, especially if it is combined with suitable remedies.

Other Minor Indications. Some French writers recommend adrenal gland alone or in conjunction with other organotherapeutic synergists in tuberculosis, paludism and cachexia.

There is undoubtedly a class of cases who unconsciously are subnormal from an adrenal standpoint (they have "minor adrenal insufficiency" just as we find "minor thyroid insufficiency"); these individuals are particularly susceptible to stress—emotional, physical or toxic, and are especially responsive to adrenal therapy.

Contraindications. Diabetes mellitus and glycosuria; vascular disease such as atheroma, aneurysm, purpura, etc.; conditions of severe sympathetic irritability (hyperadrenia) and in hypertension.

Synergists. The glandular extracts which exert a musculotonic or dynamogenic influence (gonads, thyroid, pituitary) are often given with total adrenal substance. Dynamic pluriglandular therapy is a well-established procedure.

Administration and Dosage. One-half to 2½ grains three or four times a day, before meals. In myocardial cases it may be well to give, say, one grain a day for a few days, then to increase the dose very gradually until as high as 10 grains a day are being given. In Addison's disease 5 or more grains may be given at a dose. The interrelation of these glands should be borne in mind and suitable additions to the adrenal feeding be made to make up for the other endocrine deficiencies which invariably accompany the serious disorganization of such important organs as the adrenals.

Remarks. Adrenal substance is much more gradual in its action than adrenalin, and hence must be given for prolonged periods. On the other hand, while adrenalin injections may be immediately helpful in severe hypoadrenia accompanying febrile conditions, etc., its action is very ephemeral and the ultimate benefit of such gland feeding is better. Of course both may be used simultaneously. Adrenal substance is useless in asthma.

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12. THE ADRENAL GLANDS—THE CORTEX

Source and Form. The suprarenal capsules of cattle from which the medullary portion (which has quite a different histological structure) has been removed previously. Available in powder and tablet form.

Physiologic Relations and Action. The adrenal cortex, or interrenal gland, exerts an essentially antitoxic function and also has been shown to be concerned in the control of the development of the gonads. Reports show that in Addison's disease the tissue destruction may be confined to the cortex alone. It is probable that the better effect of total adrenal substance as compared with adrenalin in Addison's disease and the control of the adrenal symptom-complex—asthenia, hypotension and malnutrition—is largely due to the corticular elements present. The

effect of adrenal feeding in gonad insufficiency, especially in elderly men, is doubtless due to the functional relationship of the adrenal cortex and the gonads.

Principal Therapeutic Indications. While rarely used alone there are a few reports in the literature telling of good effects following its use in conditions due to defective gonad development. It has been given in Addison's disease alone and to supplement total adrenal gland feeding (q. v.) and in certain osseous developmental dystrophies including osteomalacia and to hasten the retarded joining of fractures.

Other Minor Indications. Adrenal cortex has been given successfully in aspermia and it has also been recommended in developmental impotence. Based on results in such cases some have used it in functional impotence, especially in the male.

Synergists. Usually given with the medullary substance as "total gland." Theoretically it should fit in well with spermin and orchic substance, and also with corpus luteum or total ovary, especially in organic or developmental cases.

Administration and Dosage. Two to 5 or more grains t. i. d. Four grains a day was the dose used successfully in the condition of aspermia mentioned above.

Remarks. Some writers insist that the cortex of the adrenals is of greater importance than the medulla, and Biedl urges that the cortex is quite essential to life and not the medulla. Attention should be called to the peculiar clinical relationship of precocious gonad development and function in hypernephroma in children.

13. THE BLOOD—HEMOGLOBIN

Source and Form. The red blood cells of cattle, usually. Available as a fine, impalpable powder or in tablets with or without associated remedies. It is occasionally used in France in a syrup.

One liter of fresh blood contains about 167 grams of hemoglobin, while 100 parts by weight of red blood cells contains 31 per cent. of hemoglobin. (Hemoglobin represents 90 per cent. of the solids of the erythrocytes.) The percentage of actual iron is 0.336.

Physiologic Action. Hemoglobin is a natural form of organic iron and constitutes about nine-tenths of the red blood cells. It is considered to be the most easily assimilable iron obtainable. Its administration stimulates an increase in the production of hemoglobin as well as the number of erythrocytes. According to Potter, "the action of iron is to cause an increase of the hemoglobin of the red corpuscles either by its direct conversion into an ingredient of hemoglobin, or by stimulating the

functional activity of the hematopoietic organs, or perhaps by both means combined." The French insist that hemoglobin, hematin and hemochromogen are more than easily assimilable forms of organic iron, they believe that they exert a typical homostimulant organotherapeutic influence or as Potter puts it in the statement quoted above "stimulating the functional activity of the hematopoietic organs."

Principal Therapeutic Indications. All forms of anemia, including chlorosis; malnutrition; chorea; hypothyroidism, especially in weak children; syphilitic and cancerous cachexia; following operations where there has been a severe loss of blood and wherever iron medication is indicated.

Synergists. Thyroid is often useful, especially where the anemia is accompanied by signs of hypothyroidism. Spleen extract and bone marrow may be given with hemoglobin with benefit. Nucleinic acid (nuclein) is another effective synergist in reduced blood efficiency—low Hgb.-index and poor resistance to infection.

Administration and Dosage. Three to 5 grains t. i. d., before meals. As little as 1½ grains a day is claimed to render decided hematinic service.

Remarks. Hemoglobin has an advantage over the majority of iron preparations in that it does not cause constipation, and is easily and thoroughly assimilated. In the nocturnal incontinence of children (especially in the illy-nourished) a combination of hemoglobin and thyroid is likely to be effective.

14. THE BLOOD—NORMAL SERUM

Source and Form. The blood serum of healthy normal horses. It may be obtained in ampules or syringes for immediate use. Another product of blood serum is an anhydrous powder (coagulose) made by precipitating normal serum. This is soluble in water and may be obtained in powder form or in bulbs containing 1 mils. of a solution. Still another similar product is called Hemoplastin.

Physiologic Action. Certain ferments and similar substances in blood serum favor the re-establishment of more nearly normal blood conditions, especially in cases with (1) local or general infective conditions and (2) hemophilia and other manifestations of hemorrhagic disease.

Principal Therapeutic Indications. All hemorrhages due to defective clotting of the blood, including hemophilia, melena neonatorum, purpura hemorrhagica; postoperative hemorrhage; gastro-intestinal and genito-urinary hemorrhage and hemoptysis. To facilitate healing and control infection in superficial wounds and also as a tampon or pack in puerperal sepsis.

Other Minor Indications. Normal serum is occasionally used as an immune serum in certain forms of sepsis, including septic pneumonia, typhoid and acute rheumatic fever where definite antisera are not available. Used occasionally in leukemia.

Contraindications. Apparently the dangers due to anaphylaxis are now overcome, especially when one uses the nontoxic precipitate mentioned above.

Administration and Dosage. *Local:* By direct application once or twice a day—fresh serum may be used. When given to control gastric or duodenal conditions, 50 to 100 mils., by mouth, repeated as needed. *General:* 15 to 30 mils. injected subcutaneously once a day, or every six hours, depending upon the reaction to the medication, and the severity of the condition. In urgent cases the contents of two ampules (each containing 15 mils.) given intravenously, and repeated in several hours if need be.

Remarks. An increasingly valuable method of treatment in otherwise hopeless cases. The use of the redissolved precipitate seems to have entirely overcome the real dangers of anaphylaxis. It is also valuable where there is a persistent oozing following intranasal and tonsillar operations.

15. THE BLOOD—ANTITHYROID SERUM

Source and Form. The blood serum of thyroidectomized horses or sheep, taken about four or five weeks after the operation. Obtainable fresh (rarely used), in powder or in solutions of the powder.

Physiologic Action. It is presumed that after the thyroid is removed, the blood becomes surcharged with the elements normally held in check by the hormones of the thyroid. These substances are thought to neutralize the toxic products of excessive thyroid activity.

Principal Therapeutic Indications. Thyroid hypersecretion (thyroidism); Graves's disease or exophthalmic goiter; thyroid tachycardia; etc.

Synergists. Desiccated pancreas gland to antagonize the adrenal irritability common in hyperthyroidism; adrenal and pituitary substances to slow and steady cardiac action.

Administration and Dosage. Five-grain capsules of the powder are available, of which 2 to 4 may be given daily for a long period.

16. THE BLOOD—LEUCOCYTE EXTRACT

Source and Form. Prepared from a sterile exudate artificially produced in the pleural cavities of rabbits, horses or other

animals by the injection of a suitable irritant solution. The exudate is aspirated and the cellular sediment separated by centrifuging, then extracted in distilled water and incubated. Available in ampule form.

Physiologic Action. Experimental and clinical data indicate that this extract brings about a decided artificial immunity in or against various infectious diseases, due doubtless to an increase in the bacteriotropic action of the blood, as well as to the destruction of the toxins of the infecting micro-organisms. This relieves, in a measure, the overworked leucocytes and tends to protect the higher cells of the animal or person so treated, so that their functions are not deranged by the severe toxemia.

Principal Therapeutic Indications. Severe infections where a definite bacteriological diagnosis is not available—to supplement mixed bacterins in a degree. Clinical data of increasing volume is available and covers the successful treatment of erysipelas and other streptococcic infections, pneumonia (lobar and lobular), various forms of septicemia, pyemia, etc., cerebrospinal meningitis and severe constitutional infections generally.

Synergists. Hemoglobin where anemia and wasting is marked; nuclein (nucleinic acid).

Administration and Dosage. Given hypodermically usually into the abdominal wall or glutei in doses of 10 mils. once or twice a day. More frequently in extreme cases.

Remarks. This extract must not be considered as taking the place of the well-known antitoxins or vaccines. It has been recommended, however, as a very useful adjunct and may be used in connection with them in many severe infections.

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17. BONE MEDULLA

Source and Form. The medullary portion of the long bones of very young (preferably fetal) cattle. Available most commonly as a glycerinated extract; also diluted in powder and capsules.

Physiologic Relations and Action. Extract of red bone marrow stimulates the action of the hemopoietic system, increasing both erythrocytosis and leucocytosis.

Principal Therapeutic Indications. Various forms of anemia and malnutrition, including chlorosis, leukemia, post-hemorrhagic and secondary anemias. As an adjunct in the treatment of many disorders of nutrition, such as tuberculosis, Bright's disease, marasmus, etc., in which an increased production of red blood cells and their contained hemoglobin, is desirable. Bone marrow may be used alone or in conjunction with spleen extract in splenic disease, especially chronic malaria and splenomegaly.

Synergists. Hemoglobin, spleen substance, other hematinic drugs.

Administration and Dosage. One to three drams of the glycerin extract, three or four times a day in milk or carbonated water between meals. The average dose of dry extracts is 5 to 10 grains, 3 or 4 times a day.

18. THE BRAIN—LECITHIN

Source and Form. The esters of the fatty acids (stearic, oleic, etc.) with choline and phosphorus. Obtained by extraction from egg yolks or, preferably, from brain or spinal cord substance. A brownish, gum-like mass which may be dispensed in solution (glycerin), emulsions or pills.

Physiologic Relations and Action. Lecithin is extremely rich in an easily assimilable form of phosphorus and hence is a food-drug reconstructant of merit. Its introduction into medicine followed a demonstration of its growth-stimulating properties. It is said to be a cerebral and nerve tonic in certain depraved mental and metabolic states.

Principal Therapeutic Indications. Debility and malnutrition; phosphaturia; neurasthenia and "nervous prostration" and conditions sometimes called "loss of nerve energy or tone"; developmental and nutritional defects; chorea and certain forms of mental disorder; functional impotence and premature senility.

Other Minor Indications. As an adjunct in convalescence from acute infectious diseases, etc., the disorders of the climacteric, tuberculosis and marasmus. Also useful with hemoglobin in anemia, etc.

Synergists. Other dynamogenic remedies as adrenal, pituitary, etc.; hematinic products as hemoglobin, nucleinic acid and, occasionally, as an adjuvant to thyroid.

Administration and Dosage. Lecithin contains approximately 4 or 5 per cent of organic phosphorus and is given in doses of ½ to 3 grains, between meals, three times a day. This represents 1-50th to ⅛th of a grain of phosphorus per dose. Glycerin solutions are also available, each dram representing 1-25th grain of phosphorus.

Remarks. "Undoubtedly the most useful and best form of phosphorus in clinical use today." Brain and spinal cord substance (q. v.) are largely useful on account of their content of organic phosphorus.

19. THE BRAIN—THROMBOPLASTIN

Source and Form. An emulsion of the white matter of the brains of cattle in saline solution, preserved with trikresol.

Physiolcgic Action. The lipoids of brain have been shown to activate the clotting power of the blood when applied locally to the bleeding surface.

Principal Therapeutic Indications. Originally applied locally, following tonsillectomy, adenotomy and other operations. Since been extended to many other conditions of local hemorrhage and, especially, oozing. For instance, following labor where there is a persistent oozing; after curettage; in cervical carcinoma, etc. In dentistry after extensive extractions. In hemorrhage from the umbilicus, melena and purpura-like hemorrhages of earliest infancy.

Other Minor Indications. The local hemostatic value of thromboplastin (kephalin) has been used satisfactorily in vesical or reno-pelvic bleeding; for local application (per os) in gastric ulcer and (per rectum) for hemorrhoids and rectal bleeding and in certain surgical operations as breast amputation or varicose vein excision where extensive areas are opened and liable to prolonged bleeding or oozing.

Contraindications. Arterial bleeding.

Administration and Dosage. The emulsion of thromboplastin is swabbed freely on the bleeding area. A pad of gauze soaked in the emulsion may be placed upon the area. It may be replaced as often as needed. Usually one generous application suffices.

Remarks. Many thousands of cases of tonsillectomy and adenotomy have been routinely treated (by the N. Y. City Department of Health) with prophylactic swabbing with thromboplastin, and there can be no doubt of its real hemostatic virtues.

20. THE KIDNEYS

Source and Form. The glomerular substance of the kidneys of cattle, sheep or hogs. Usually available in powder or tablets.

Physiologic Relations and Action. The kidneys are stated to exert a certain specific neutralizing effect in toxemia, with a special influence upon those irritating substances in the blood which affect the kidney glomeruli. It is also said to be a diuretic by acting upon the secretory activity of the tubules of the kidneys.

Principal Therapeutic Indications. Various forms of renal insufficiency including ischuria, anuria, albuminuria and some forms of Bright's disease; in ascites and dropsy due to renal disorder; as an adjunct in uremia.

Other Minor Indications. It has been incidentally noted that kidney extract not only frequently reduces albumin, but also increases the urea output quite considerably.

Administration and Dosage. Five to 10 grains of desiccated kidney substance in capsules or tablets, three times daily at or immediately after meals. Fresh minced kidneys have been given, but the dry powder is much better tolerated.

21. THE LIVER

Source and Form. The parenchymatous tissue of the liver of cattle or hogs. Available in powder or tablets.

Physiologic Relations and Action. The liver, in addition to regulating metabolism, plays an important part in the control of detoxication and from a clinical standpoint, at least, seems to be concerned in the regulation of blood coagulation.

Principal Therapeutic Indications. The homostimulant action has been used with success in functional hepatic insufficiencies as well as such organic manifestations as atrophic cirrhosis, alcoholic liver, etc. It is also used as an adjunct in cholelithiasis. Its detoxicating powers make it of possible utility in such diseases as gout, rheumatism, etc. Its remarkable antihemorrhagic influence has been used to good advantage in controlling hemoptysis in pulmonary tuberculosis; and in France liver extract is commonly used in the treatment of this disease for in addition to its antihemorrhagic action there is claimed to be a specific detoxicating value which is frequently referred to. It is also used to control other local hemorrhages including hemoptysis, epistaxis and the minor manifestations of hemophilia, petechiae, etc.

Other Minor Indications. There is a form of diabetes in which a disturbance of the function of the liver is prominent for which desiccated liver has been recommended. This form, however, is not nearly so common as pancreatic diabetes, and in this latter liver extract seems to aggravate the symptoms. In mucous colitis, especially with bile salts.

Contraindications. Pancreatic diabetes.

Synergists. Bile salts, spleen substance and, occasionally, thyroid extract.

Administration and Dosage. In France where this therapeutic procedure originated, the dose recommended in well-defined hepatic disorder is one to four grams (15 to 60 grains) of desiccated liver substance just before meals three or four times a day. In less severe conditions a fraction of this amount is effective.

22. THE LYMPHATIC GLANDS

Source and Form. The lymph nodes of young cattle. Available in powder or tablet form. (Very hygroscopic.)

Physiologic Relations and Action. It has been presumed by some writers that the quite constant enlargement of the tonsils and growth of adenoids in children at a certain age, was a protective act on the part of the body—it required certain substances proliferated in these glands in increasing quantity. The use of preparations of lymphatic glands is merely an attempt to supplement this seemingly necessary activity of the lymphoid tissues of the body.

Principal Therapeutic Indications. In children from five to ten years where the tonsils are enlarged, adenoids are present with the usual associated symptoms. In such cases the mouth breathing and the general nutrition, as well as the size of the enlarged glands were all benefited. Snoring was very often stopped. Also used in the so-called "lymphatic type" of children who are poorly nourished, have enlarged glands in the neck, adenoids, etc., and who bleed easily.

Other Minor Indications. Lymphatic substance is being recommended in "worn-out" individuals as a reconstructive measure in conjunction with spermin, etc. It is hard to say how much benefit it may bring about in such cases.

Synergists. Thyroid, especially in "lymphatic" children where hypothyroidism is present; spleen; spermin (in senility); calcium salts in hemophilia.

Administration and Dosage. One half to one grain of the dried glandular substance, gradually increased to 5 grains, t. i. d.

Remarks. This method of treatment of children has been tried by a number of physicians, and seems to be deserving of more extended consideration, especially in children known to be backward as a result of lymphatism, adenoids, etc. In France lymphatic extract is recommended for adenitis, tuberculous adenitis and other similar conditions.

23. THE PANCREAS—TOTAL GLAND

Source and Form. The acinous tissue of the pancreas of cattle or hogs. Available in powder or soluble extract.

Physiologic Relations and Action. The pancreas in addition to its all-important digestive functions is an important gland of internal secretion the chief function of which is to facilitate the metabolism of carbohydrates. (See Islets of Langerhans.) This gland also appears to exert a very definite antagonistic effect upon the adrenal hormone, in fact Sir Edward Schaefer insists on calling the pancreatic endocrine principle a "chalone" or anti-hormone because of its opposing effect.

Principal Therapeutic Indications. The principal value of total pancreas substance is to antagonize hyperadrenia. Hence its utility in infections where adrenal irritation by bacterial and

other toxins is marked. Functional hypertension may be due to adrenal irritability in which case the pancreas extract may exert a distinct depressor effect. In pancreatic disease it may be given for its homostimulant effect.

Other Minor Indications. Of value in a form of infantilism described by Bramwell. Also in conditions of lowered resistance to infection, boils, ulcers, etc., it may be given as a rational adjunct measure. In Graves's disease it sedates the irritability of the sympathetic system through its anti-adrenal action.

Synergists. In hypertension, small doses of thyroid. In infections, nuclein. In Graves's disease adrenal substance and pituitary (posterior).

Administration and Dosage. Two to ten or more grains given three or four times a day, preferably between meals. The solution is practically only used in experimental work.

24. PANCREAS—ISLETS OF LANGERHANS

Source and Form. The splenic end or tail of the pancreas. (Approximately 90 per cent of the islands of Langerhans are to be found in this location.) Powdered substance or glycerinated extract from which the enzymes which may be present have been removed. Trypsogen is the best-known remedy of this type.

Physiologic Relations and Action. The internal secretion of the pancreas has been called by v. Noorden "the brake to the sugar factory," and, indeed, it exerts a remarkable influence on carbohydrate metabolism either by its antagonism to the capacity of the liver to release sugar (it is generally believed that the adrenal medullary hormone stimulates this, and it is well known that this chromaffin hormone is a direct antagonist of the Langerhansian hormone), or that the internal secretion of the pancreas is directly concerned in facilitating the burning of sugar in the muscles, etc. It also reduces blood pressure.

Principal Therapeutic Indications. Diabetes mellitus of pancreatic origin. To antagonize adrenal excess in high blood pressure of alimentary origin. The homostimulative action may be of benefit by favoring the re-establishment of the normal work of the pancreas.

Other Minor Indications. A theory has been advanced by Little which offers some hope of practical application. He uses an extract containing the internal secretion of the pancreas in the treatment of cancer of organs originating in the same blastodermic layer—the endoderm. (See also Total Pituitary and Adrenal Cortex.)

Contraindications. In diabetes due to hepatic disorder pancreatic organotherapy seems to aggravate the trouble.

Administration and Dosage. There is no definite information regarding dosage for there is no known way of knowing to what extent the internal secretion of the pancreas is deficient. Small quantities of the powder—1 to 2 grains—may be given before meals, and the dose increased at intervals of a few days until 10 or 15 grains are being taken three times a day. Trypsogen is given in doses up to 7 five-grain tablets three times a day. It must be taken for a long period. Cases have taken it for years and seem to benefit by it in a manner quite similar to cretins taking thyroid extract.

25. THE PARATHYROIDS

Source and Form. The parathyroid glandules of cattle or, occasionally (in France), horses. The desiccated gland is used in capsules or tablets, and a repurified nucleo-proteid solution is also obtainable which may be given by mouth or hypodermically.

Physiologic Relations and Action. The parathyroids control the destruction of toxic substances which have a special predeliction for attacking the nervous system. They are also intimately concerned in the maintenance of calcium metabolism. Their total removal rapidly causes death, which is accompanied by tetany and a serious loss of calcium by the body.

Principal Therapeutic Indications. Parathyroid insufficiency with marked nervous irritability and tetany, either due to inadvertent partial parathyroidectomy (in goiter operations) or to parathyroid disease; to act as a detoxicator in certain conditions manifested by nervous and, especially, convulsive conditions such as tetany—spontaneous, postoperative, gastric and infantile; epilepsy; etc. It is principally used in the treatment of Parkinson's disease (paralysis agitans) and its persistent use causes a reduction in muscular rigidity and tremor, and also favors better muscular control of the facies and gait. It also seems to sedate the restlessness and insomnia, a change for the better which is frequently noted quite early in the treatment. It is said that an obvious degree of benefit may be expected in as much as 80 per cent. of the cases thus treated.

Other Minor Indications. Parathyroid therapy has been recommended in Italy for eclampsia, uremia and for toxic convulsive conditions generally. It has been suggested as of possible value in certain motor neuroses including myoclonia. It has also been used in chorea.

Administration and Dosage. The nucleo-proteid solution (Berkeley) is given hypodermically once daily in doses of 1-50th grain. It may be given in the same dose by mouth, two or three times a day. Desiccated parathyroid gland is probably used more

commonly, the average dose being 1-10th to 1-20th grain two or three times a day.

Synergists. Hepatic substance; bile salts and preparations from either gonads; atropin by mouth, 1-200 grain per dose or less and, of course, hyoscine hydrobromide as a myosedative.

Remarks. Parathyroid therapy is not usually effective unless persisted in for months and, like many other phases of organotherapy, is purely an adjuvant measure.

26. THE PLACENTA

Source and Form. The placentae of sheep or cows, preferably the former. Available in powder or tablets.

Physiologic Relations and Action. The placenta is fairly well established as having an internal secretion, and extracts of it as exerting a certain physiological activity. It favors uterine involution and lactation and, generally, the re-establishment of normal conditions after the puerperium. In this connection it will be remembered that many animals have the habit of devouring the afterbirth, presumably for some definite purpose.

Principal Therapeutic Indications. In agalactia it often causes an increase in the production of milk. In pernicious vomiting of pregnancy it often causes remarkable results after many other remedies had failed. It has also been recommended to prevent atrophy of the uterine walls after ovariotomy and to favor uterine involution in chronic hyperplastic metritis due to infection, etc., after labor.

Synergists. Mammary gland; pituitary (total).

Administration and Dosage. Three to 10 grains four or more times a day, before meals. In pregnancy give before sleep or with hypnotic drugs, if necessary, to prevent its loss.

Remarks. The antiemetic value of placenta in hyperemesis gravidarum is explained on a basis similar to the antigen-amboceptor neutralization, i. e., the ingested substance contains bodies which neutralize the poisons of pregnancy and also favor the production by the body of increasing amounts of this neutralizant. About half an ounce, all told, suffices. If this dosage (covering ten days) is unsuccessful, it is useless to continue it.

27. THE PITUITARY BODY—TOTAL GLAND

Source and Form. The complete pituitary body (all lobes) from cattle. Obtainable in powder or tablet form.

Physiologic Relations and Action. The therapeutic action of total pituitary extract is essentially the combined action of the extracts of the two lobes which it includes. It is a general muscular tonic and, in a lesser degree than the posterior

extract, a vascular stimulant, reducing atonicity of unstriped muscle, including that of the heart and intestines. It is also claimed to be a useful physiologic diuretic; though, strangely, its administration has successfully controlled diabetes insipidus.

Principal Therapeutic Indications. To control some of the manifestations of definite pituitary disease; reducing the neuralgic pains, apathy and lethargy, and also the hemianopsia not uncommonly found in this condition. Useful in certain developmental disorders where anterior pituitary (q. v.) is indicated, including infantilism, adiposity and Fröhlich's syndrome. Because of its hypertensive action it has been used in Addison's disease with fair results. Available as a useful general tonic alone or with adrenal extract in conditions where the blood pressure is low, such as tuberculosis, malnutrition, asthenia, typhoid and other severe febrile conditions, etc. In cardiac asthenia it reduces the tachycardia and increases the tension. In anuria it is reported to have caused satisfactory diuresis, though here one would prefer an injection of the posterior lobe principle, as, for instance, *Liquor Hypophysis, U. S. P.,* (Harrower).

Other Minor Indications. Exerts a stimulant effect upon digestion and alimentary peristalsis (due to its musculo-stimulant action) and may be given with other synergistic extracts. It is also of value in "run-down" states, particularly when combined with small doses of thyroid. Little suggests that total pituitary substance may be a useful adjunct in the treatment of cancer in organs of ectodermic origin.

Synergists. Thyroid; ovary or testes; thymus.

Administration and Dosage. One half to one grain after meals and at bedtime. Occasionally, especially in definite pituitary disease, 5 grains or more may be given t. i. d.

Remarks. This extract is not used as much as it deserves to be, presumably because it has been recommended in the substitution therapy of pituitary disease (just as thyroid therapy was for many years limited to definite athyroidic cases) or, perhaps, because its therapeutic action has been entirely overshadowed by the rapid rise of posterior pituitary extracts due to their remarkable activity. It is, none the less, a valuable general tonic in many varying conditions.

28. THE PITUITARY BODY—ANTERIOR LOBE

Source and Form. The pituitary gland proper, or pars anterior of the hypophysis of cattle. Used in powder and tablet form.

Physiologic Relations and Action. The anterior lobe of the pituitary is a definite gland of internal secretion, and is con-

cerned in the control of development and metabolism. Unlike the infundibulum (posterior lobe), it can not be removed without causing death. Experimental work shows that its partial removal or disease brings about a condition of adiposity, asexualism and reduced bodily activities, including subnormal temperature and marked asthenia.

Principal Therapeutic Indications. Functional pituitary dystrophies, including infantilism (especially the obese type), delayed mental development in children with mental obtundity. Also very useful in the treatment of certain amenorrheas, especially in obese girls and young women, as well as in asexual individuals and those manifesting other evidences of partial infantilism. Certain forms of epilepsy.

Other Minor Indications. Recommended in the treatment of diabetes insipidus. Recently suggested as a useful remedy for bronchial asthma.

Synergists. Thyroid and gonads.

Administration and Dosage. One to 5 grains, 3 to 6 times a day, usually given between meals in capsule or tablet form. In asthma 2½ grains q. i. d. for several weeks.

Remarks. The value of this preparation is being more and more appreciated by those who have to treat mental and physical mal-development in children. Its other possibilities when more fully established will doubtless bring it into more general use.

29. THE PROSTATE GLAND

Source and Form. The prostate glands of cattle or horses. Available in powder, tablet or liquid form.

Physiologic Relations and Action. Used purely for its homostimulant action. It is also said to exert a diuretic action which is probably due to an influence upon the urinary passages, rather than upon the secretion.

Principal Therapeutic Indications. Prostatic hypertrophy with retention, strangury, frequent micturition, etc.; chronic prostatorrhea; as an adjuvant in the treatment of specific and non-specific infections of the prostate; following prostatectomy and in the so-called "neurasthenia of prostatic origin."

Other Minor Indications. Also recommended with spermin and testicular substance, since prostatectomy frequently causes functional testicular inactivity.

Synergists. Testicular substance (spermin); lymphatic gland; thyroid.

Administration and Dosage. Three to 5 grains t. i. d., after meals. Occasionally increased to 10 grains at a dose.

Remarks. An opinion is gaining ground that some forms of prostatic hypertrophy are of a compensatory nature since they usually occur when gonad function is on the wane. It has been definitely helpful in such circumstances.

30. THE SPLEEN—TOTAL EXTRACT

Source and Form. The splenic parenchyma from calves, pigs or sheep. The fresh substance has been highly recommended and liquid preparations of it are occasionally used. It is most often given in powder or tablets.

Physiologic Relations and Action. The spleen is said to bring about the activation of the trypsin in the white blood cells, thus favoring phagocytosis. It activates tryptic digestion (Schiff) and Bayle says that the spleen contains a "colloidogen" which favors the maintenance of the mineral elements of the body in their natural colloid state, thus preventing their elimination as wastes. The spleen is also the source of an active peristaltic hormone (q. v.) which, however, seems to be produced elsewhere and only stored up in the spleen.

Principal Therapeutic Indications. Spleen insufficiency as in paludism and severe forms of malarial toxemia, splenomegaly and spleen cirrhosis. Used as an adjunct measure in malnutrition and pulmonary tuberculosis, with anemia and demineralization. (This influences nutrition rather than the actual control of the infective process.) Also used occasionally in bone and glandular tuberculosis.

Other Minor Indications. Spleen extract is a valuable hematinic. A solution has been recently recommended in pernicious anemia and hypodermic injections for several weeks are said to have secured moderately good results.

Synergists. Thyroid; hepatic substance; hemoglobin; nuclein; etc.

Administration and Dosage. Five to 15 grains, q. i. d., after meals. May also be given hypodermically, in which case 1 or 2 mils. of a specially prepared solution are given daily. In tuberculosis Bayle recommends injection of 5 mils. into the glutei each day for 12 days, a rest for 8 days; another series of 12 injections, followed by another rest of 8 days, etc. Fresh spleen may be given in doses of one or two ounces with soup, jam or other disguising substances, twice a day at meals.

Remarks. Spleen extract is not a useless remedy, but is used as an adjunct in diseases of nutrition and particularly tuberculosis. Some French writers call it a most useful factor in increasing weight and nutrition in certain forms of tuberculosis, especially pulmonary.

31. THE SPLEEN—PERISTALTIC HORMONE

Source and Form. The spleen tissue from cattle or hogs, at the height of digestion when killed. A preparation, Hormonal, was on the market in ampules.

Physiologic Relations and Action. The peristaltic hormone discovered by Zuelzer is produced in the stomach and duodenum and stored up in the spleen, hence it is not really a "splenic hormone." It exerts a remarkable influence upon the intestinal musculature and blood supply, the enteric vessels being temporarily engorged with a large amount of blood, very shortly after the injection. Blood pressure is thus reduced.

Principal Therapeutic Indications. Acute paretic conditions of the intestines, including postoperative inactivity or paralysis, with obstipation, meteorism, etc. Chronic constipation, etc.

Contraindications. Spastic constipation, shock and vasomotor instability.

Administration and Dosage. Intravenous injection; 20 mils., given very slowly (15 minutes). Preferably in hospital practice. Intramuscular injection: 20 to 40 mils. of a special preparation, with an analgesic, it is understood. Usually given half in each buttock. One treatment usually suffices. For children in proportion.

Remarks. Posterior pituitary preparations have practically superseded this product as their administration is not accompanied by such severe vasomotor changes. Hormonal treatment has caused a number of reported deaths, which were presumed by Zuelzer and others to be due to proteid poisoning. The preparation is now freed from these albuminoids, but still has no obvious advantage over Liquor Hypophysis.

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32. THE TESTES

Source and Form. The testicles of rams or bulls. Available in powder or tablet form, and also in solution for injection. One part of dried substance represents from 7 to 9 parts of the fresh gland, depending upon the age of the animal.

Physiologic Relations and Action. The testes contain a chemical element called "spermin" which is intimately concerned in the control of nutrition, oxidation and the cell activities generally. It is the "dynamogenic hormone."

Principal Therapeutic Indications. Infantilism, cryptorchism and congenital malformations of the testes. Functional testicular insufficiencies including sterility, debility, premature senility and impotence. Useful as an adjunct in sexual neuroses and neurasthenia; defective oxidation and reduced cellular activity; and certain disorders of growth and mentality.

Other Minor Indications. Testicular or orchic substance has been used with success in amenorrhea, and in the hot ovary flashes and other allied disturbances of the menopause in women. It causes results quite similar to corpus luteum, sometimes, indeed, where this latter has been given without much success, especially in infantile uterus.

Synergists. Small doses of thyroid; total adrenal gland; prostate gland; lymphatic gland.

Administration and Dosage. Three to 10 grains after meals and at bedtime. It is advisable to start with a small dose and gradually to increase the amount. Hypodermic injections have been recommended, but have no special advantage over the products given by mouth, and often cause quite painful proteid reactions.

Remarks. A preparation of the interstitial cells of Leydig (the essential endocrine portion of the testes and presumably equivalent to the corpora lutea of the ovaries) is available, and is particularly rich in spermin.

33. THE THYMUS GLAND

Source and Form. The thymus glands of calves, preferably from fetal animals. Given in powder and tablet form.

Physiologic Relations and Action. The thymus exerts a decided influence upon the mineral metabolism, especially of calcium. Sajous states that in addition to controlling the growth of bone, the thymus also regulates phosphorus metabolism. Stimulates the hemopoietic organs and the lymphatic glands. Regulates the growth and activities of the essential sexual organs in childhood. The gland ceases to function and is supposed to disappear a short time before puberty.

Principal Therapeutic Indications. Malnutrition, delayed development in children and disorders in which the mineral metabolism is disturbed, especially rachitis. In exophthalmic goiter its use has been frequently followed by a reduction in the tumor and improvement in the exophthalmos as well as the circulatory and nervous manifestations. Chronic joint disturbances including rheumatoid arthritis have been treated with advantage by several writers, but medication must be persistent and systematic; particular attention has been called to the value of this method in controlling severe joint pains.

Other Minor Indications. Certain blood dyscrasias including chlorosis; as an adjunct in tuberculosis with anemia; certain lymphatic disorders.

Synergists. In lymphatic cases calcium salts and lymphatic gland; in Graves's disease anterior pituitary gland; in arthritis small doses of thyroid.

Administration and Dosage. Five or more grains, 4 to 6 times a day, preferably some time after meals. Should be given in gradually increasing amount and continued for weeks or months.

34. THE THYMUS GLAND—NUCLEINIC ACID

Source and Form. Nucleinic acid, sodium nucleinate or nuclein is a definite chemical substance found in the nuclei of certain living cells. Originally it was obtained from the thymus, later from egg-yolks, fish roes, milk, brain tissue and yeast. At present the chief source is yeast, though sodium tritico-nucleinate is made from the germ of wheat. It is available in a yellowish-white powder or in solution.

Physiologic Action. It exerts a remarkable leucocyte-stimulating effect, increasing resistance to infection by augmenting the anti-bacterial powers of the blood. Following injections of solutions there is a noticeable hyperleucocytosis, which is rightly presumed to supplement the normal defenses thru the increased phagocytosis thus brought about.

Principal Therapeutic Indications. As a means of increasing the defensive powers of the blood in acute or chronic infections or the infectious diseases. Used with benefit in erysipelas, pneumonia, septicemia, typhoid fever, quinsy, etc. In chronic infections, especially of the asthenic type, as tuberculosis, it may be useful. In anemia and general debility, following malaria and infectious arthritis. It improves nutrition in rickety children. Its dynamogenic cell-stimulating capacity and its faculty of "increasing the vigor of the central nervous system" makes it a beneficial adjuvant in the organotherapeutic treatment of hypogonadism and conditions of senile cellular asthenia, especially where a latent infection may be present.

Synergists. Nuclein reinforces organotherapy very nicely. It may be given with thyroid, ovarian (or testicular) or adrenal substances. It has been added to combinations for the treatment of prostatic disease, senility, etc., with tangible advantage. It also goes well with Hemoglobin.

Administration and Dosage. By mouth alone or with other indicated remedies in doses of ⅛ to ½ grain, three or more times a day. Injections are usually somewhat painful due to the local reaction (hyperleucocytosis also around area of injection), and there may be a temporary febrile reaction immediately following. Nuclein solution contains 6 grains of sodium tritico-nucleinate to the ounce. The dose is 10-60 minims.

Remarks. The reconstructant and stimulant effect of nucleinic acid is indeed valuable, and this remedy deserves to be used more frequently, especially in conjunction with indicated organotherapeutic remedies.

CLASS C: EXTRACTS USED LESS FREQUENTLY

35. THE APPENDIX

Source and Form. The mucous membrane of the appendices of hogs. Secured in desiccated powder or glycerinated extract. One part equals 12 parts of the fresh scrapings.

Physiologic Relations and Action. The appendix is said to produce a substance which stimulates peristalsis and the cecal reflex.

Principal Therapeutic Indications. Constipation; digestive disturbances following appendectomy; intestinal stasis.

Administration and Dosage not yet thoroughly established.

Remarks. Appendicular extract is only used experimentally and casually mentioned in a few French communications.

36. BONE

Source and Form. The long bones of various animals, from which the organic matter has been removed. Available in powder form. (Some physicians prefer pulverized fresh bone substance in a glycerinated emulsion, with or without suitable adjuvant medicaments.) A preparation of partially digested "Green Bone" from chickens is also on the market.

Physiologic Relations and Action. The mineral salts secured from bones are said to be more easily appropriated by the system, and their administration is claimed to have some influence upon the nutrition and mineral metabolism.

Principal Therapeutic Indications. Conditions in which demineralization is common; tuberculosis, malnutrition, phosphaturia, after parturition, in rachitic children, and in other metabolic dyscrasias.

Administration and Dosage. Ten to 40 grains or more, with meals.

Remarks. The same salts from other sources should be of equal benefit, i. e., the "remineralization treatment" is of real value and not to be deprecated because of the statements of some that the actual bone salts are "far superior." It is probable that a properly prepared bone emulsion, including red bone marrow, might prove of considerable service in suitable cases.

37. THE BRAIN AND CORD—TOTAL SUBSTANCE

Source and Form. The brain matter, spinal cord and nervous tissue of sheep. Defatted powders representing about five

times the amount of fresh substance and total emulsions (see Thromboplastin) are obtainable.

Physiologic Action. Brain and nerve substance contains lecithin which is a really valuable therapeutic agent. Some writers insist that the total extract causes a stimulation of the mental and nervous activities, favors detoxication and is an anti-convulsant of value.

Principal Therapeutic Indications. Mental and nervous disorders, including depression, melancholia, hysteria, epilepsy, neurasthenia, etc. As an adjuvant to remedies as adrenal gland, spermin, etc.

Administration and Dosage. One to 3 grains of the defatted powder, three or four times a day, between meals. One to three drams of the emulsion, before meals.

38. THE LUNGS

Source and Form. Lung tissue from very young animals, for preference, lambs. Desiccated in powder form.

Physiologic Action. There is said to be a principle in lung extract which exerts a tonic action upon the whole respiratory tract, especially upon the bronchial mucosa and the pulmonary alveoli.

Principal Therapeutic Indications. Brunet and a few French investigators have recommended lung extract in all chronic diseases of the lungs and pleura, especially those of a purulent character. This included chronic bronchitis, purulent pleurisy, lung abscess, etc. It has also been used with mediocre results in phthisis, bronchial asthma and emphysema.

Administration and Dosage. Dried extracts are given in moderately large doses—10 to 20 grains, 4 to 6 times a day—for months.

Remarks. A ferment called "thrombokinase" which has a decided antihemorrhagic influence, is made from fresh lung tissue. Its value does not seem to be greater than that of blood serum, coagulose, etc., and this last has virtually supplanted it.

39. THE PAROTID GLAND

Source and Form. The parotid glands of cattle. Available in powder or tablet form.

Physiologic Relations and Action. The parotid is evidently also a gland of internal secretion and intimately related to certain of the ductless glands, as evidenced by the frequency with which orchitis, ovaritis, pancreatitis, etc., follow mumps.

Principal Therapeutic Indications. Parotid extract was originally used in the treatment of pelvic troubles in women,

especially ovaritis, dysmenorrhea and ovarian neuralgia. It has also been recommended in conditions where the menses are irregular and there is considerable pain at the periods. It might also be of service in the reflex inflammatory sequelae of mumps.

Administration and Dosage. Two to 8 grains, t. i. d., before meals, continued for some time.

Remarks. Parotid extract is practically never used, now that we have a much more effective and physiologic remedy in ovarian extract and corpora lutea which have entirely superseded it. It might be that where luteal extract does not bring about the desired results, particularly where there is ovarian inflammation and much pelvic pain, parotid extract might be given in conjunction with it; 2 grains of parotid to 5 of ovary, repeated every three or four hours before the expected flow, and more frequently during severe menstrual pains.

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40. THE PINEAL BODY—(EPIPHYSIS)

Source and Form. The pineal glands from young cattle. The total gland is triturated and dispensed in powder or tablet form. "It takes approximately 5000 pineal glands of cattle to make one pound of the available extract."

Physiologic Relations and Action. The pineal gland, presumed for a long time to be a rudimentary organ without function, is now known to have a definite physiologic action, especially in childhood and early youth. Disordered pineal function produces quite marked changes in metabolism, which result in a hastening of maturity—physical, mental and sexual; although some writers have intimated that this gland holds these very functions in abeyance until puberty.

Principal Therapeutic Indications. Clinically, pineal gland has been used in the treatment of mentally deficient children without physical stigmata. This includes the not infrequent cases where the mental activity is below par with no obvious organic changes. It has also been recommended in mongolism.

Other Minor Indications. It has been suggested that pineal gland might be of some value in cases of premature mental failure without a distinct organic cause—to "stimulate the aging brain to faster chemistry."

Contraindications. While pineal gland substance is not toxic, it is useless to give it with expectation of results in children over 10 or 12; and in cases of idiocy with anatomical brain or gonad defects.

Administration and Dosage. Half to 1 grain of the triturate three times a day. It must be given systematically for four to six months.

41. THE STOMACH—GASTRIN

Source and Form. Scrapings from the mucosa of the pyloric antrum from hogs. Made in a manner essentially similar to secretin. It has been produced experimentally in powder and glycerinated extract which contains the gastric secretin (gastrin).

Physiologic Relations and Action. Gastrin is said to activate (in a manner quite similar to the duodenal secretin) the peptic and oxyntic glands of the stomach as well as to favor the production of increased quantities of the precursors of gastrin in the cells of the pylorus. Its action is practically identical to that of secretin.

Principal Therapeutic Indications. Gastric insufficiency; apepsia, hypopepsia, dyspepsia, etc.

Contraindications. Hyperpepsia, gastric ulcer, etc.

Administration and Dosage. Not yet well defined—1 to 5 grains of the desiccated scrapings have been given, before meals.

Remarks. The experimental and clinical work with gastrin is by no means as extensive and convincing as that with secretin, and since this latter seems to have a very satisfactory influence upon the indigestions in general, it is used much more frequently.

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42. THE TONSILS

Source and Form. The tonsils of calves or other young animals. At present the watery extracts alone have been used, and no preparations are yet on the market.

Physiologic Relations and Action. Strangely enough, the tonsil is the most active of all the organic extracts (Ott). It temporarily reduces blood pressure and is stated to exert a glycolytic action. It is said also to favor an increase in both the red and white blood cells.

Principal Therapeutic Indications. Tonsil extract has been used in clinical therapeutics only by a few investigators in Italy in the treatment of diabetes. It is also of possible value in anemia. Tonsil extract is "able to arrest the fatal toxic action of epinephrin."

Administration and Dosage. Hypodermic or intramuscular injections of watery infusions may be made, the dose depending chiefly upon the weight of the animal treated. In clinical work no dose has yet been worked out.

SECTION III. PART 2

STOCK PLURIGLANDULAR FORMULAS

A number of fundamental forms of pluriglandular therapy are represented by a series of "stock formulas" made in my laboratory. These formulas constitute a well-considered effort to apply the essential principles of organotherapy to several fairly large groups of cases. Each of these pluriglandular prescriptions has been used repeatedly, and it is with a confidence born of results—sometimes unexpected results—that they are recommended here.

The following statements embody the essential information regarding these stock formulas. In Section V, "Every-day Organotherapy," further consideration is given to various phases of the subject. Additional explanatory literature regarding several of these preparations is available on request, and the writer has accumulated a quantity of enthusiastic complimentary statements which are published from time to time, copies of which also will be sent to interested physicians.

The prescriber is advised to call for a full box of 100 capsules, since organotherapy is an attempt to re-establish some function, and 24 or 36 capsules accomplish virtually nothing. The prices mentioned in this book are *net*, but include the delivery charges. It is desirable to specify "Harrower," at least until the pharmacist is acquainted with the products of this laboratory.

Finally, since the routine administration of certain of these formulas, especially, for instance, the Thyro-Ovarian combination, calls for a more or less extended signature on the prescription, it may be found convenient to use the following form: "Sig. Take as usual," in which case the pharmacist who carries these products and has access to this information will insert the signature which has been printed following each "Sig."

Attention is again called to the fact that no trade names are used, the formulas are neither secret nor ambiguous, and the labels contain no indications nor the boxes any explanatory circulars. In other words, *every effort has been made to be as ethical and professional as possible.*

NO. 1. CAPS. ADRENO-SPERMIN COMP.

ASTHENIA; Hypotension; Neurasthenia; Hypoadrenia.

Formula: Each capsule contains five grains of the following combination: Adrenal substance total gr. ¼, Thyroid gland (U. S. P. IX) gr. 1/12, Spermin extract (from gonads) and Brain substance (lecithin) aa gr. 1 with Calcium Glycerophosphate q. s.

Prescribe Thus: ℞ Caps. Adreno-Spermin Co. (Harrower) No. C. Sig. One q. i. d. just before meals and at bed time. (In

acute cases and under special circumstances, one every three hours.)

Price: Boxes of 100, $2.50.

Physiological Effects: A support to depleted adrenal function, hence a means of reducing neuro-muscular asthenia due to hypoadrenia. Increases sympathetic tone, stimulates oxidation and increases "dynamos." An organotherapeutic tonic and reconstructant.

Indications: Chronic asthenic conditions with deficient oxidation (low urinary elimination) such as accompany chronic toxemia and follow acute infectious diseases, especially influenza, pneumonia, etc. The "fatigue syndrome" and run-down states with low blood pressure, cardiac and circulatory insufficiency (cold extremities) and subnormal temperature. Many functional neuroses including neurasthenia, psychasthenia, melancholia, etc.

Remarks: Should be given early in acute conditions as a prophylactic against the expected "let down," which is almost invariably an adrenal syndrome. Continue for 3 or 4 weeks, beginning with 1 every 3 hours, ending with 1, t. i. d. In chronic asthenias the blood pressure is an excellent guide both as to dosage and length of administration. A. B.P. (systolic) of 110 mm. calls for 1, t. i. d., of 100 mm. 1, q. i. d. and 90 mm. or less 1, 5 or even 6 times a day. The longer the symptoms have persisted the larger the initial dose and the longer the treatment—up to 3 or more months.

Reference: Sec. IV, Ch. 5; Sec. V, Ch. 1, 2, 5 and 18.

NO. 2. CAPS. ANTERO-PITUITARY COMP.

DEFECTIVE CHILDREN; Maldevelopment; Cretinism; Epilepsy.

Formula: Each capsule contains five grains of the following combination: Pituitary gland (anterior lobe) gr. 2; Thymus gland. gr. 1; Thyroid gland (U. S. P. IX) gr. 1/12 with Calcium Phosphorus Co. (see No. 11) q. s.

Prescribe Thus: ℞ Caps. Antero-Pituitary Co. (Harrower) No. C. Sig. One twice a day at meals, for 4 out of every 5 weeks. Continue for several months. (In larger children, and later in the treatment, an additional dose may be advisable.)

Price: Boxes of 100, $3.75.

Physiological Effects: A growth stimulant (morphogenic) and endocrine regulator in defective development—hypoplasia—in children and youths. Found to have a favorable influence on petit mal and epilepsy for reasons not well defined, presumably due to a hypopituitaric factor in the etiology of these conditions.

Indications: Children with obvious endocrine deficiencies —thyroid, pituitary, etc. Retarded mentality (so-called "backward children" with or without decided stigmata), deficient growth, mongolism, dwarfism, etc. Epilepsy, petit mal, chorea and indefinite disorders which may be associated with or due to dyscrinism. As a means of broadening the use of thyroid in cretinism.

Remarks: Results have been both remarkable and unexpected, while, on the other hand, this formula has been often used in organic cases with definite cerebral defects with no benefit whatever. This cannot be determined in advance, so this treatment is often a "last straw" which is well worth trying. Must be given with the understanding that results are possible but not necessarily probable, and also that it is useless to give it for less than 4 to 6 months. Small doses—2 or 3 capsules a day—for long periods are better than larger doses for a shorter time.

Reference: Sec. IV, Ch. 7; Sec. V, Ch. 7 and 8.

NO. 3. CAPS. PLACENTO-MAMMARY COMP.

GALACTAGOGUE; Post-partum stimulant; Uterine involutant.

Formula: Each capsule contains five grains of the following combination: Desiccated placenta gr. 2, Mammary substance gr. 1½, Pituitary body (total) gr. ⅓ with Calcium Phosphorus Co. q. s.

Prescribe Thus: ℞ Caps. Placento-Mammary Co. (Harrower) No. C. Sig. Two capsules at meals three times a day for first 10 days, thereafter one three times a day.

Price: Boxes of 100, $3.50.

Physiological Effects: Mammary stimulant, galactagogue; post-partum regulator by favoring uterine involution. Beneficial influence upon infant's weight and nutrition.

Indications: Deficient or poor milk secretion, agalactia, hypogalactia. Infantile malnutrition. Preferably as a prophylactic especially in mothers whose previous nursing experiences were not good.

Remarks: Push the dosage for the first period, then reduce the dose until at three weeks or a month it may be omitted. In some cases it has been given throughout the whole nursing period, since its omission caused a return of the hypogalactia within a few days. It has been noted that the use of this formula seems to inhibit menstruation during the nursing months, a distinct advantage both to mother and child.

Reference: Sec. V, Ch. 4 and 14.

NO. 4. CAPS. THYRO-OVARIAN COMP.

DYSOVARISM; Amenorrhea; Dysmenorrhea; Neurasthenia; Menopause.

Formula: Each capsule contains five grains of the following combination: Ovarian substance (total) with Corpus luteum gr. 2½; Thyroid gland (U. S. P. IX) gr. 1/12; Pituitary body (total) gr. ⅛ with Calcium Phosphorous Co. q. s.

Prescribe Thus: ℞ Caps. Thyro-Ovarian Co. (Harrower) No. C. Sig. One t. i. d., a. c. for 10 days, double dose for 7 to 10 days before menses, omit at onset of menses for 10 days. Repeat. (In total amenorrhea: 1, t. i. d. for 10 days, 2, t. i. d. for 2 weeks; omit a week; repeat.)

Price: Boxes of 100, $3.50.

Physiological Effects: Ovaro-uterine regulator through the endocrine function of the ovaries and also the associated synergistic ductless glands.

Indications: Amenorrhea (delayed, scanty, absent or difficult menses); dysmenorrhea; sterility; sexual apathy; numerous neuroses and psychoses connected with the menstrual function. Climacteric disorders and circulatory imbalance of ovarian endocrine origin.

Remarks: This is one of the most efficient endocrine remedies. The fact that the associated endocrine glands are taken into consideration (for it may well be that the whole trouble is not so much ovarian as thyroid or pituitary, as both physiology and clinical experience has repeatedly shown) has made the use of this formula helpful when corpus luteum or ovarian substance alone had been tried previously for long periods without results. The cyclic method of administering suggested above is much more satisfactory than the usual "one or two, t. i. d."

Reference: Sec. IV, Ch. 8, Sec. V, Ch. 3, 8 and 18.
The booklet "Ovarian Dysfunction" and other literature explains the philosophy of this method and tells of many encouraging clinical experiences with it.

NO. 5. CAPS. HEPATO-SPLENIC COMP.

INTESTINAL STASIS; Hepato-biliary Insufficiency; Alimentary Toxemia; Malnutrition.

Formula: Each capsule contains five and a half grains of the following combination: Hepatic parenchyma and desiccated spleen substance aa gr. 2, Bile Salts (powdered) gr. ½ with Adreno-Spermin Co. (No. 1) gr. 1.

Prescribe Thus: ℞ Caps. Hepato-Splenic Co. (Harrower) No. 3. Sig. One capsule after each meal and at bed time. (In certain instances the dose may be doubled and continued for weeks.)

Price: Boxes of 100, $3.00.

Physiological Effects: Alimentary stimulant and regulator through the liver and spleen mechanism, as well as through the general endocrine system. A means of encouraging the secretory and detoxicative powers of the liver. Not by any means a cathartic, save in very large doses.

Indications: Hepato-biliary insufficiency and sluggishness, resulting in intestinal stasis and toxemia. Hepatic cirrhosis. Malnutrition of long-standing, toxic origin, especially in cachexia, tuberculosis, malaria, etc.

Remarks: It seems that this organotherapeutic formula goes deeper than one expects of an ordinary hepatic stimulant. There is a support, a sort of physiological encouragement, which is more satisfactory than the usual "liver medicines." It should be remembered that this preparation exerts an educative influence and should be continued for some time, especially in the chronic cases of alimentary laziness.

Reference: Sec. V, Ch. 2 and 5.

NO. 6. CAPS. PANCREAS COMP.

SYMPATHETIC IRRITABILITY; Hyperthyroidism; Heart Hurry and Cardiac Weakness.

Formula: Each capsule contains five grains of the following combination: Adrenal and Pituitary glands (total) aa gr. ½, Ovarian substance gr. 1 and Pancreas gland (total) gr. 3.

Prescribe Thus: ℞ Caps. Pancreas Co. (Harrower) No. C. Sig. One capsule q. i. d., between meals. (In acute cases, especially in severe hyperthyroidism, the dose may be increased to 6 or 8 capsules a day for a short time.)

Price: Boxes of 100, $2.50.

Physiological Effects: A cardiac muscular support and sedative. Functional antagonist to sympathetic irritability, especially that due to excessive thyroid secretion. Ovarian content suggested by Crotti, since dysovarism is so common in such cases. (No objection to using same formula in men, however.)

Indications: Irritable, irregular, rapid and weak pulse, especially of endocrine origin. Nervousness and irritability resulting from hyperthyroidism. Post-influenzal and other toxic asthenias with a susceptible thyroid.

Remarks: A sympathetic sedative and useful remedy in hyperthryoidism, but with practically no direct influence upon the causative factors in this disease. Must be used with other measures, especially those calculated to antagonize or remove (1) sources of toxemia (teeth, tonsils, sinuses, colon, gall bladder, pelvis or elsewhere), (2) dyscrinism especially disturbed functions of the ovaries or a persistent thymus or (3) emotional and

psychic conditions which may and do unduly stimulate the thyroid and adrenal glands. An excellent means of preparing a case of toxic goiter for indicated surgery, and a worth while remedy in severe toxemias where more radical measures are contraindicated.

Reference: Sec. V, Ch. 6 and 18.

NOS. 7, 8, 9. CAPS. THYROID COMP. GR. ⅛, ¼, ½

HYPOTHYROIDISM; Myxedema; Cretinism; Minor Thyroid Insufficiencies.

Formula: Each capsule contains five grains of Calcium Phosphorus Co. (see formula of No. 11) with one-eighth, one-quarter or one-half a grain of U. S. P. (IXth edition) Thyroid gland, respectively.

Prescribe Thus: ℞ Caps. Thyroid Co. (Harrower) gr. ⅛ (or ¼ or ½, as desired) No. C. Sig. One capsule t. i. d. before meals.

Price: Boxes of 100, $1.75. (Same price for Nos. 7, 8 & 9.)

Physiological Effects: Supplementary organotherapy in functional or organic thyroid secretory insufficiency. Remineralization. (See No. 11.)

Indications: Hypothyroidism — myxedema, with lesser forms of thyroid insufficiency, manifesting various degrees of infiltration (of skin, mucous membrane and tissues generally), suboxidation, obesity, dermatoses or ovarian dystrophies. Cretinism, with maldevelopment, mental backwardness, mongolism, etc. In many nutritional disorders with metabolic insufficiency and defective elimination.

Remarks: The addition of the mineral salts to thyroid extract is based on sound reasoning, and clinical experience emphasizes its value. Thyroid extract is practically always given in the hope of increasing cell chemistry, for any degree of hypothyroidism, from the least to the most serious, always entails reduced metabolism and a consequent excessive production of acid wastes which automatically rob the organism of its alkaline reserve. This explains the acidosis and cellular poisoning which is the rule in thyroid insufficiencies, and at the same time supplements the thyroid gland stimulation by means of remineralization or restoring the alkaline mineral salts that have been depleted. Hence the excipient, used instead of milk sugar or starch, may be as therapeutically useful as the thyroid itself.

Reference: Sec. IV, Ch. 2 and 3.

NO. 10. THYROID TESTING CAPSULES

THYROID TEST; Differential Diagnosis of Goiter; Estimation of Thyroid Secretion.

Formula: Each small box (of which there are three in each package) contains twelve graduated capsules of thyroid

extract, four small, four medium and four large, representing one-half, one and two grains of U. S. P. Thyroid, respectively.

Prescribe Thus: ℞ One Thyroid Test (Harrower), with chart. Sig. Follow printed instructions carefully.

Price: Single tests on prescription, 60c. Packages of 3 tests, $1.25.

Physiological Effects: A routine, step-ladder thyroid function stimulant, bringing about a reaction which varies in different individuals in proportion to the thyroid sensitiveness or apathy, which may be recorded upon a pulse chart which serves for comparison between different cases, or the same case under different circumstances. A means of measuring thyroid functional activity.

Indications: In all forms of simple goiter and where thyroid enlargement is not obviously due to a well-established hyperthyroidism. As a differential diagnostic measure between goiter due to thyroid secretory incapacity or overstimulation. As a means of discovering a latent thyroid sensitiveness without goiter. Also valuable in the study of metabolic dyscrasias, as obesity, rheumatism, etc.—where it is presumed that a thyroid element may be present, and where thyroid stimulation properly may be added to the treatment if the test shows the need for such treatment.

Remarks: A simple and extremely convenient measure—the physician has only to hand the package to the patient or prescribe it, as the instructions are minutely outlined with the chart which accompanies the test—which places thyroid medication upon a rational basis, instead of the administration of this remedy haphazard and until the patient complains of the untoward reaction due to overstimulation of the gland. Not alone useful in goiter and presumed thyroid troubles, but especially worth while in the study of disturbed cell chemistry, in ovarian disorders, in nutritional disturbances and in many cases where the discovery of thyroid irritability or apathy, as the case may be, would offer a new angle from which to consider and treat the case.

Reference: Sec. IV, Ch. 4 and Ch. 12, Sec. V, Ch. 5.

NO. 11. TABS. CALCIUM PHOSPHORUS COMP.

DEMINERALIZATION; Hyperacidity (Acidosis or Acidemia); Toxemias.

Formula: Each tablet contains 15½ grains (one gram) of the following combination: One hundred parts represents Magnesium Phosphate 2, Calcium Phosphate (dibasic) and Calcium Glycerophosphate aa 8, Potassium Bicarbonate 32 and Sodium Bicarbonate q. s.

Prescribe Thus: ℞ Tabs. Calc. Phosphorus Co. (Harrower)

No. C. Sig. 3 tablets, crushed, with much water, twice a day, one hour before food.

Price: Boxes of 100, $1.50.

Physiological Effects: Neutralizes systemic acid wastes. Replaces the alkaline mineral reserve, depleted by poor oxidation and abnormal production of acid or, at least, "alkaline robbing" products. This condition of mineral depletion is known in France as "demineralization" and the therapy as "remineralization."

Indications: Particularly useful in the adjunct treatment of chronic toxemic conditions, especially those so commonly associated with endocrine insufficiencies (notably of the thyroid gland—see Nos. 7, 8 and 9). Indicated in a large list of chronic disorders in conjunction with gland feeding and other measures.

Remarks: The above formula (with the addition of sodium chloride) contains the mineral salts in the approximate proportions present in the blood, and is the standard excipient in The Harrower Laboratory. In many cases it is advisable to push the dosage for the first few weeks of the treatment with pluriglandular therapy and this non-glandular "mineral food" was added to the list since it is so commonly and definitely useful in these conditions. At least six grams a day should be given to an adult during the first two or three weeks of treatment, the dose then being reduced to, say, four grams every other day, or less often, depending upon conditions which may be present.

Reference: Sec. V, Ch. 6 and 16.

NO. 12. CAPS. AMYLO-TRYPSIN COMP.

INDIGESTION; Flatulence; Gastric Dilatation; etc.

Formula: Each capsule contains five grains of the following combination: Amylopsin (pancreatic diastase) gr. ½, Pancreatin (U. S. P. IX) gr. 2½, Papain gr. ½, Berberine sulphate gr. 1/12 and a mixture of Cinnamon, Nutmeg and Jamaica Ginger, q. s.

Prescribe Thus: ℞ Caps. Amylo-Trypsin Co. (Harrower) No. C. Sig. Two capsules, two hours after eating.

Price: Boxes of 100, $2.50.

Physiological Effects: The first three ingredients further the digestion of proteid and starch, according to principles well established in physiological chemistry. Berberine is the yellow alkaloid of golden seal (and also the barberry) and is an efficient mucosal tonic; while the excipient consists of the well-known plant carminatives. A polyenzyme, tonic digestant formula.

Indications: Gastro-intestinal indigestion with achlorhydria, flatulence and fermentation. Wherever alimentary en-

zyme medication is called for, especially in atonic gastric insufficiency.

Remarks: The ferments are active and cooperate with one another. No pepsin is present but in its place papain (so-called "vegetable pepsin" which is active in either acid or alkaline media) is used. Each package contains a card on which is printed the following:

Note: The digestive ferments in these capsules are destroyed by heat above 110 deg. F. It is advisable to take them some hours after eating, with water. Do not take with HOT foods or drinks.

The digestive capacity is maintained best when the capsules are kept DRY. In damp climates, after breaking the seal, it may be advisable to transfer to a dry, well-corked bottle.

NO. 13. CAPS. HEMOGLOBIN COMP.

ANEMIA; Chlorosis; Malnutrition.

Formula: Each capsule contains six grains of the following combination: Hemoglobin (repurified) gr. 4, Desiccated spleen parenchyma gr. 1, Acid Nucleinic (Nuclein) gr. ½ with Calcium Phosphorus Co. q. s.

Prescribe Thus: ℞ Caps. Hemoglobin Co. (Harrower) No. C. Sig. One capsule before meals and on retiring. (Considerably increased doses may be given when marked hematinic effects are needed, say, three capsules, four times a day for a week or more.)

Price: Boxes of 100, $3.00.

Physiological Effects: Purveys an acceptable and easily absorbable iron to the organism. Non-constipating. Stimulates hematopoiesis. Encourages leucocyte production and phagocytosis.

Indications: All forms of anemia, both primary and secondary. Malnutrition due to blood conditions; convalescence from acute infectious diseases, surgery and the puerperium, especially where there has been a considerable loss of blood. Cachexia, cancer and chronic blood destroying conditions including pernicious anemia. Where iron ordinarily is indicated.

Remarks: An unusually excellent combination which has been the means of causing a number of remarkable changes in the Hgb. index and blood picture. It should be stated that this or any other form of iron exerts no known influence upon the blood-cell-destroying factor in pernicious anemia. The French insist that hemoglobin, in addition to its hematinic virtues, also exerts a "homostimulant action" similar to the influence of thyroid extract upon thyroid secretion, etc. At all events it is quite the best form of iron for oral administration.

Reference: Sec. V, Ch. 9.

NO. 14. CAPS. NUCLEO-LECITHIN COMP.

MALNUTRITION; Cachexia; Marasmus; Rickets; etc.

Formula: Each capsule contains seven and a half grains (half a gram) of the following combination: Lecithin (90-95%) gr. 2½, Acid Nucleinic (Nuclein) gr. 1, Calcium glycerophosphate and Calcium phosphate (dibasic) aa gr. 2.

Prescribe Thus: ℞ Caps. Nucleo-Lecithin Co. (Harrower) grs. viiss, No. C. Sig. Three capsules a day, with food. (Larger doses may be taken, say, up to two capsules four times a day.)

Price: Boxes of 100, $4.50.

Physiological Effects: Each of the ingredients of this formula contains organic phosphorus in easily assimilable form, in fact lecithin is stated to be the richest and most easily acceptable form of organic phosphorus known. Each capsule cotnains a generous dose of this product, as well as of nuclein and the glycerophosphate of calcium.

Indications: Malnutrition, especially in such chronic or developmental dystrophies as are known to respond particularly to phosphorus, including certain central nervous disorders, cachexia, marasmus and rickets. A reconstructive and nutritive nerve and cell tonic.

Remarks: Lecithin is a remarkable remedy and for many years has been warmly recommended for a very much longer list of disorders, mostly of a chronic and nerve type, than is mentioned above. The combination is as good a phosphorus bearing one as the writer knows of, and each individual element therein is generously dosed.

Reference: Sec. III, Part 1-B.

NO. 15. CAPS. SECRETIN COMP.

INDIGESTION; Pancreatic and Biliary Insufficiency; Intestinal Toxemia.

Formula: Each capsule contains five and a half grains of the following combination: Secretin extract (duodenal) gr. 3, Bile salts (powdered) gr. 1½, Adrenal substance gr. ¼ with Calcium Phosphorus Co. q. s.

Prescribe Thus: ℞ Caps. Secretin Co. (Harrower) No. C. Sig. Two capsules between meals, t. i. d. It may be well to push the dosage to 3 or even 4 capsules per dose for the first week or 10 days in intractable cases. In ordinary instances and to maintain the effects for a longer time in cases of long standing 1, t. i. d. may suffice.

Price: Boxes of 100, $2.50.

Physiological Effects: Secretin stimulates pancreatic, biliary and intestinal glandular secretion, and actually forms a part

of the finished enzymic products. Bile salts encourage increased biliary production. Adrenal gland is a tonic to unstriped muscle as well as to alimentary activity as a whole.

Indications: Chronic indigestion with toxemia, stasis, constipation and the numerous direct and indirect results thereof. Hepato-alimentary insufficiency with fetid, clay-like stools. Pancreatic insufficiency. Hypochlorhydria.

Remarks: Quite unlike the enzyme products commonly used in various forms of indigestion. Secretin is the normal, physiological hormone stimulus of practically all of the digestive secretions; it has been recommended for some years as an efficient and physiological remedy. In the digestive crises in summer complaint of children, the contents of one-half to one capsule with food, t. i. d., is a useful dose. In the digestive disorders of tabes, pregnancy and cancer, especially the latter, where it will be recalled there is practically no HCl in the gastric secretion—and HCl is the natural excitant to secretin production in the duodenal mucosa, this formula is definitely indicated.

Reference: Sec. V, Ch. 5, 13 and 15.

NO. 16. LIQUOR HYPOPHYSIS (U. S. P.)

PARTURITION; Hemorrhage; Shock; Stasis & Meteorism; Enuresis; Polyuria; Epilepsy; etc., etc.

Formula: Each milliliter of the sterile, standardized solution of the active infundibular principle of the pituitary body, corresponds approximately to .02 gm. of the fresh gland.

Prescribe Thus: ℞ Liq. Hypophysis (Harrower) 15 mils. (½ oz.) (For physician's or hospital use only.)

Price: Vials of 15 mils., $2.50. (Twelve ampules each containing 1 mil. will be supplied for the same price on special request *to California.*)

Physiological Effects: Stimulant of unstriped muscle, including heart, intestines, etc., and, especially, of the pregnant uterus. Homostimulant to the pituitary. Regulator of diuresis. Galactagogue.

Indications: As above and outlined later. As discussed previously under "Pituitary Body—Posterior Lobe."

Dosage: *Hypodermic*—Do not inject *superficially.* In Labor: Early (before dilatation of the cervix) 2 minims, diluted. At completion of dilatation, 5-15 min. Repeat in 30 to 45 minutes, if needed. After Labor: Once daily for 2 to 4 days (antihemorrhagic, involutant, intestinal stimulant, galactagogue, diuretic!) In Surgery: 8-15 min. before operation, repeat (during long operations) after 2 hours, otherwise at each of three intervals of 6 to 8 hours. (To prevent shock, hemorrhage, meteorism, etc.) In Nose and Throat Surgery: 5-15 min. one

hour prior to tonsillectomy, etc. (5-8 min. in children) prevents hemorrhage and shock. In Cardiac Asthenia and Failure: 5-8 min. daily or more often. In Graves's Disease: 5-10 min. twice daily; later once daily and still later once every other day. In Intestinal Paresis: (with stasis, alimentary cramps and meteorism) 15 min., repeat in 3 or 4 hours, if needed. In Obstipation: 5 min.; after 2 hours, 10 min.; after 4 hours more, 15 min.; after still another 4 hours, 15 min., if needed. (Give to effect.) In Enuresis: 5-8 min. every other day for 2 weeks; double this dose for adults. In Epilepsy: 10-15 min. (less in children) daily, or every other day for several weeks, followed later, perhaps, by 15 min. once a week for some months in conjunction with *Caps. Antero-Pituitary Co.* (No. 2, q. v.) In Diabetes Insipidus: 10-15 min. daily or e. o. d. for 8 or 10 doses.

Oral Administration. Twice the stated hypodermic dose, twice or three times a day, in the chronic phases of conditions mentioned above; as: Before surgery, in cardiac disease, Graves's disease, alimentary stasis and atony, enuresis and epilepsy. Useless *per os* in labor, shock, severe obstipation and active conditions where immediate results are necessary.

Intravenous Injection. In serious collapse, cardiac failure, hemorrhage and where the indicated hypodermic use is ineffective, give 15-30 min. (1 or 2 mils.) with 20 mils. or more of sterile saline solution into the median basilic vein. Repeat in 2 hours, if desirable.

Remarks: "A very wonderful and unexcelled remedy in a surprisingly large and varied list of disorders."

The physiological efficacy of this preparation is rigidly standardized in harmony with the requirements of the U. S. P. IX and the recommendations of the Treasury Department of the U. S. In addition to careful checking in the laboratory, a portion of each batch is sent east for restandardization in a prominent research laboratory. It is stable, sterile and standard. The vial package developed in The Harrower Laboratory favors rapidity of use, convenience in securing smaller or larger doses than the usual ampule contents and, hence, economy.

Instructions: Remove vial from protecting box. Bare the rubber covering. Alcoholize this and the sterile needle. Dry thoroly. Insert needle thru rubber. Invert. Withdraw *just enough* of the solution—*DO NOT RETURN ANY EXCESS.* Replace cover. Return to container.

Reference: Sec. III, Part 1, No. 8.

SPECIAL EXPERIMENTAL COMBINATIONS

As has been explained elsewhere, the original object of the writer in establishing this laboratory is to broaden organother-

apy; and in my opinion this ideal will be reached more quickly and with less difficulty by developing the relationships between the endocrine glands and the advantages of combining their products, than in any other way. In addition to the "Stock Formulas" already mentioned, a large number of "Special Formulas" have been prepared for numerous interested physicians. These have been used, and modified and made again and again. The most effective of these formulas are mentioned here. They are known to have been definitely serviceable in certain cases, though they are not as frequently used and advised as the previously mentioned stock preparations. If desired, any formula, either stock or special, will be changed to suit the ideas of any physician.

Some of these formulas represent important advances and much work has been done to develop them, and more detailed information regarding the various subjects may be had on request. The data which follow are very brief and, if additional special information is desired, a communication to the laboratory (in California) will bring it whenever this is possible.

S. F. NO. 18. CAPS. IODIZED THYROID COMP.

GOITER; Simple Thyroid Enlargement; Hypothyroidism.

Formula: Each capsule contains six grains of the following combination: Thyroid gland (U. S. P. IX), Ferrous Iodide, Acid Nucleinic (Nuclein) aa gr. ¼ with Calcium Phosphorus Co. q. s.

Prescribe Thus: ℞ Caps. Iodized Thyroid Co. (Harrower) No. C. Sig. One, t. i. d. between meals with water. (Occasionally best to give four to six capsules a day for a short time.)

Price: Boxes of 100, $3.25.

Physiological Effects: Replaces the deficient thyroid hormone, stimulates thyroid secretory activity. The iodine is a thyroid stimulant (food) and nucleinic acid reinforces the whole by furthering the immunity and leucocytic functions.

Indications: Simple goiter or enlargement of the thyroid with no evidence of thyroidism (best to have previously made a Thyroid Function Test—see No. 10—and differentiated between thyroid enlargement due to glandular insufficiency and that due to glandular irritability); anemia and malnutrition, especially in girls at puberty who have slight enlargement of the thyroid; hypothyroidism with or without enlargement of the gland.

Remarks: Where thyroid enlargement is due to an attempt of the body to meet certain unusual demands for the thyroid stimuli, the gland is enlarged to render the larger service demanded of it. This is also true where there is a thyroid cellular inefficiency with the usual demands of the organism for its influence on metabolism. In girls at puberty and women during

the various ovarian changes there often appears an enlargement of the thyroid which is benefited by such treatment as is represented by this special formula. It serves the double purpose of offering a suitable dose of thyroid and a convenient form of iodine (which, by the way, has the added advantage of the hematinic value of the iodide of iron) plus the leucocyte and resistance-stimulating effect of nuclein.

Reference: Sec. IV, Ch. 4.

S. F. NO. 22. CAPS. BILE SALTS COMP.

BILIARY INSUFFICIENCY; Mucous Colitis; Constipation; Intestinal Indigestion.

Formula: Each capsule contains three grains each of repurified powdered bile salts and desiccated hepatic substance.

Prescribe Thus: ℞ Caps. Bile Salts Co. (Harrower) No. C. Sig. One q. i. d. between meals for 3 days, then double dose for 3 more days, then treble dose for 3 days, continue until free bile appears with stool, then reduce to 3 caps. a day for some weeks. (It is well to repeat this step-ladder routine monthly, especially in old and stubborn cases.) Note: It is best to give written instructions to the patient direct as the dose varies naturally with the hepato-biliary response and the above routine is infinitely superior to the usual method, therefore I suggest this direction to the pharmacist: Sig. Take increasing doses between meals as directed.

Price: Boxes of 100, $2.50.

Physiological Effects: Hepato-biliary stimulant, increasing both the flow of bile and the general hepatic activity including its detoxicative functions. Favors the re-establishing of normal conditions in muco-membranous entero-colitis.

Indications: Functional liver insufficiency, intestinal stasis, sluggish bile flow, gall stones, duodenal indigestion and chronic nutritional disorders such as tuberculosis where hepato-biliary function is especially important. Mucous colitis. Chronic hepatic disease with cirrhosis or hypertrophy.

Remarks: The clinical value of bile is not appreciated enough. It is the cholagogue *par excellence.* Hepatic substance has been used for years in France to facilitate the re-establishment of deficient liver activity. The above combination is superior to either of the ingredients.

The proper dosage is "enough." If constipation is marked and the patient is taking cathartics, continue them as before. Suggest the above step-ladder dosage and when free bile is seen omit the cathartics, continuing the high dosage of the Bile Salts Co. for two or three days and gradually reduce it, until, perhaps, just 2 or 3 capsules are taken at night. In chronic, toxic cases I recom-

mend the repetition of this routine several times and the continuance of this treatment for months.

In France Prof. Roger insists that mucous colitis is largely a disorder due to biliary sluggishness and explains his reasons very satisfactorily.

Reference: Sec. V, Ch. 5, 7 and 13.

S. F. NO. 23. CAPS. PANCREATIN-BILE COMP.

INTESTINAL INDIGESTION; Biliary Insufficiency; etc.

Formula: Each capsule contains two grains each of Pancreatin (U. S. P. IX), Bile salts and Hepatic substance (as in No. 22).

Prescribe Thus: ℞ Caps. Pancreatin-Bile Co. (Harrower) No. C. Sig. Two capsules an hour or more after each meal. (Later this may be given in smaller doses or after only the two main meals.)

Price: Boxes of 100, $3.00.

Physiological Effects: Digestant, hepato-biliary regulator and general alimentary secretory stimulant.

Indications: Intestinal indigestion with hepato-biliary torpor, alimentary toxemia and stasis. Essentially the same indications as suggested for S. F. No. 22.

Remarks: Perhaps the addition of the pancreatin makes the combination more suited for the control of conditions in which the intestinal rather than the hepatic element predominates, especially where the stools are malodorous and often light colored and sticky.

S. F. NO. 24. CAPS. PARATHYROID COMP.

PARALYSIS AGITANS; Tetany; Hypoparathyroidism.

Formula: Each capsule contains five grains of the following combination: Desiccated Parathyroid glands gr. 1/20, Spermin Extract (from interstitial cells of Leydig) gr. 1, Bile salts (powdered) gr. 1½ with Calcium Phosphorus Co. q.s.

Prescribe Thus: ℞ Caps. Parathyroid Co. (Harrower) No. C. Sig. One capsule four times a day between meals.

Price: Boxes of 100, $3.75.

Physiological Effects: Stimulates the detoxicative influence of the parathyroids (which is said to have the faculty of destroying poisons which have a predeliction for the nervous system); increases muscular tone and stimulates hepato-biliary activity, all of which are helpful in Parkinson's disease.

Indications: Parathyroid insufficiency, including certain neuro-muscular disorders as paralysis agitans, tetany and chorea.

Remarks: Parathyroid therapy has been frequently recommended in paralysis agitans and undoubtedly it has been helpful in many cases, but I do not urge it with the enthusiasm that I recommend many other formulas from this laboratory. At least this formula is superior to parathyroid alone for two reasons: (1) There is a well-established functional relation between the liver and parathyroids and in paralysis agitans there is invariably need for hepato-biliary stimulation, (2) the cellulo-tonic effect of spermin is useful in all cases of waning glandular activity, senility and deficient oxidation.

The treatment must be given for many months, and it would be better not to start than to give a couple of hundred capsules alone. Sometimes double the above dosage for one out of every three weeks is an advantage.

Reference: Sec. IV, Ch. 10.

S. F. NO. 26. CAPS. ADRENO-HYPOPHYSIS COMP.

ASTHMA; Bronchial Asthma.

Formula: Each capsule contains five grains of the following combination: Adrenal Gland (total) gr. ½, Pituitary Gland (anterior lobe) gr. 2, Calcium Lactate and Calcium Phosphate (dibasic) aa q.s.

Prescribe Thus: ℞ Caps. Adreno-Hypophysis Co. (Harrower) No. C. Sig. One q.i.d. before meals and at bedtime. (Occasionally a larger dose may be given, say, one every three hours or two, t.i.d.)

Price: Boxes of 100, $3.75.

Physiological Effects: Antagonizes asthenia and hypoadrenia; is said to exert a beneficial effect (both because of the adrenal, pituitary and calcium content) on bronchial asthma and allied conditions.

Indications: Asthma and bronchial asthma in children and adults, especially where there may be an underlying endocrine element present.

Remarks: This formula is purely experimental. It has prospects of real value. The dosage suggested is inocuous and is not known to cause unpleasant reactions. Such a preparation cannot take the place of antispasmodic remedies like morphine or adrenalin, which may have to be used simultaneously. This remedy, however, may make some favorable modification of the underlying cause of the asthma. It is at least worth trying in suitable cases, in conjunction with other indicated measures.

Reference: Sec. V, Ch. 17.

S. F. NO. 29. CAPS. THYRO-PANCREAS COMP. with SPERMIN

S. F. NO. 30. CAPS. THYRO-PANCREAS COMP. with OVARY

FUNCTIONAL HYPERTENSION.

Formulas: Each capsule contains five grains of the following combinations: Pancreas gland (total) gr. 2, Thyroid gland (U. S. P.) gr. 1/12, Spermin extract (or Ovarian substance, respectively) gr. 2 with Calcium Phosphorus Co. q.s.

Prescribe Thus: ℞ Caps. Thyro-Pancreas Co. c. Spermin (or Ovary) (Harrower) No. C. Sig. One q.i.d., at meals and bedtime.

Price: Boxes of 100, $3.75.

Physiological Effects: Antagonist to adrenal irritability and functional irritation of blood pressure regulating mechanism, stimulant of oxidation and regulator of gonad function. In the male the spermin acts by stimulating cell activity, while in the female the ovarian substance is helpful by regulating ovarian endocrine function, especially at or after the menopause.

Indications: High blood pressure where it is evident that the sole cause is not renal, cardiac or vascular (arterio-sclorosis).

Remarks: Numerous clinical tests checked by careful sphygmomanometry have proved that the use of these formulas does reduce functionally high tensions. In organic hypertension there may be a functional element as well as the structural change, here this treatment may be given with the prospect of causing some slight reduction in the tension. If it is given for a month or six weeks with no obvious benefit, it is not likely that it would be beneficial to continue its use.

Reference: Sec. V, Ch. 10.

S. F. NO. 35. CAPS. NUCLEIN-HEMOGLOBIN COMP.

CONVALESCENCE; Malnutrition; Post-febrile Asthenia.

Formula: Each capsule contains five grains of the following combination: Acid Nucleinic (nuclein) gr. ¼, Lecithin (95%) gr. 1, Spermin extract (Leydig cells) gr. 1 with repurified Hemoglobin q.s.

Prescribe Thus: ℞ Caps. Nuclein-Hemoglobin Co. (Harrower) No. C. Sig. Two capsules q.i.d. for first week, then one, q.i.d., before meals.

Price: Boxes of 100, $4.25.

Physiological Effects: Encourages leucocytosis and favors increased immunity; supplies phosphorus in its most easily assimilated form and iron in an acceptable, non-constipating form. The spermin exerts its usual dynamic or musculo-tonic influence.

Indications: Following the exanthemata and acute infectious diseases, operations and in convalescence generally, es-

pecially in children and young people where there is malnutrition, anemia and a temporary nutritional lapse.

Remarks: A preparation like this combines several purely physiological stimulative (nutritional) effects all of which are especially needed following any severe illness, particularly during the growth period in children and adolescents. It is superior, because more rational, to the old-fashioned tonics like Beef, Iron & Wine or I. Q. & S. Its administration for a few weeks augments those essential nutritive functions which have been deranged by the fever and toxemia from which the patient is convalescing.

Reference: Sec. V, Ch. 9.

S. F. NO. 38. CAPS. MAMMA-OVARY COMP.

DYSOVARISM; Menorrhagia; Prolonged Menses.

Formula: Each capsule contains five grains of the following combination: Mammary substance gr. 2½, Ovarian substance gr. 1, Thyroid gland gr. ⅛ with Calcium Phorphorus Co. q.s.

Prescribe Thus: ℞ Caps. Mamma-Ovary Co. (Harrower) No. C. Sig. One t.i.d. a.c., double 3 days before and during menses, omit for one week. Repeat.

Price: Boxes of 100, $3.75.

Physiological Effects: Ovarian regulator, antagonist to excessive ovarian endocrine function.

Indications: Moderate menorrhagia with or without dysmenorrhea; difficult menstrual onset; too frequent menses or prolonged menses; dysovarism with a tendency to ovarian irritability and pelvic congestion.

Remarks: The best results from this formula are obtained when it is pushed just before and during the flow. In disturbed ovarian functioning sometimes this formula may be alternated with Caps. Thyro-Ovarian Co. or may replace it in ovaro-uterine conditions which lean toward menorrhagia in which the results from this latter stock formula leaves something to be desired.

Reference: Sec. V, Ch. 14 and 18.

S. F. NO. 39. CAPS. MAMMA-ERGOTIN COMP.

MENORRHAGIA; Menopausal Hemorrhages; Uterine Cancer.

Formula: Each capsule contains five grains of the following combination: Mammary substance gr. 3, Ergotin (Bonjean) gr. ¾ with Calcium Phosphorus Co. q.s.

Prescribe Thus: ℞ Caps. Mamma-Ergotin Co. (Harrower) No. C. Sig. One t.i.d. a.c., double 3 days before and during menses, omit for one week. Repeat. (Occasionally a still

larger dose may be given during the height of the flooding, say, 2 capsules every three hours.)

Price: Boxes of 100, $4.00.

Physiological Effects: Antagonist to ovarian endocrine hyperfunction; uterine muscular tonic.

Indications: Menorrhagia, functional or organic i. e. from hyperovarism, uterine fibroids or carcinoma.

Remarks: Virtually similar to S. F. No. 40 (q. v.). Same remarks apply.

Reference: Sec. V, Ch. 14.

S. F. NO. 40. CAPS MAMMA-PITUITARY COMP.

MENORRHAGIA; Metrorrhagia; Uterine Subinvolution; Fibroids; etc.

Formula: Each capsule contains five grains of the following combination: Mammary substance gr. 2½, Ergotin (Bonjean) gr. ½, Pituitary gland (total) gr. ¼ with Calcium Phosphorus Co. q.s.

Prescribe Thus: ℞ Caps. Mamma-Pituitary Co. (Harrower) No. C. Sig. One t.i.d. a.c., double 3 days before and during flow, omit for one week. Repeat. (Occasionally more may be given during the heaviest part of the flow, say, 2 capsules every three hours.)

Price: Boxes of 100, $4.25.

Physiological Effects: Antagonist to ovarian endocrine function; uterine muscular tonic; uterine circulatory depletant.

Indications: Menorrhagia, metrorrhagia and prolonged or excessive menstrual or climacteric uterine hemorrhages. Uterine fibroids.

Remarks: The above formula has been used with benefit in organic uterine disease, seemingly permanent in fibromata and temporary in cancer. The chief benefit is shown by the controlled bleeding, though quite often a fibroid will be materially reduced in size. When given for the uterine oozing of cancer, an explanation should be made that the expected benefit is symptomatic. In menorrhagia of ovarian origin this is not merely a symptomatic regulator of the excessive flow, but it is simultaneously modifying the underlying conditions responsible for the hemorrhage.

Reference: Sec. IV, Ch. 8; Sec. V, Ch. 14 and 18.

S. F. NO. 41. CAPS. LEYDIG CELL COMP.

PROSTATIC HYPERTROPHY; Impotence; Hypogonadism.

Formula: Each capsule contains five grains of the following combination: Spermin extract (from the interstitial cells of

Leydig) gr. 2½, Thyroid gland (U. S. P.) gr. 1/16 with Calcium Glycerophosphate and Calcium Phosphorus Co. aa q.s.

Prescribe Thus: ℞ Caps. Leydig Cell Co. (Harrower) No. C. Sig. One q.i.d. a.c.

Price: Box of 100, $3.75.

Physiological Effects: Homostimulant of gonads and essential endocrine function of these glands; antagonist to functional prostatic hypertrophy. Cell stimulant in impotence and senility.

Indications: Prostatic hypertrophy not due to present infection or adenoma; prostatic hyperesthesia; asthenia of gonad origin; impotence and deficient gonad function; senility.

Remarks: Originally prepared for the experimental control of simple prostatic hypertrophy on the assumption that when gonad function is on the wane the prostate may take up certain of its endocrine functions vicariously and become enlarged in a compensatory fashion. Results seem to have established its value, reduced prostatic hyperesthesia lessened micturition and a general feeling of well-being having followed the use of this formula for a month or six weeks.

Reference: Sec. V, Ch. 11.

S. F. NO. 43. CAPS. LYMPHATIC COMP.

LYMPHATISM; Hemophilia; Malnutrition; etc.

Formula: Each capsule contains six grains of the following combination: Desiccated lymphatic glands gr. 2, Spleen substance gr. 1½, Thyroid gland (U. S. P.) gr. 1/16 with Calcium lactate q.s.

Prescribe Thus: ℞ Caps. Lymphatic Comp. (Harrower) No. C. Sig. Two capsules with food, t.i.d. Dose may be reduced after 10 days or more, should be continued for fully a month.

Price: Boxes of 100, $4.25.

Physiological Effects: Hematinic; stimulant of the coagulative capacity of the blood; cellular constructant.

Indications: Badly nourished, anemic children with a tendency toward hemorrhage. Certain forms of hypothyroidism, with or without additional doses of thyroid gland. Lymphatic enlargement (see also S. F. No. 82).

Remarks: Used chiefly for children, though not contraindicated in adults of the lymphatic, "bleeder" type. May be given to such for a week or more before an anticipated operation (give an injection of *Liq. Hypophysis U. S. P.* (Harrower) half an hour before operation, also).

Reference: Sec. III, Part 1-B.

S. F. NO. 47. CAPS. PITUITARY COMP.

HYPOPITUITARISM; Infantilism; Hypogonadism.

Formula: Each capsule contains five grains of the following combination: Pituitary gland (total), Pituitary gland (anterior lobe) aa gr. 1½ with Calcium Phosphorus Co. q. s.

Prescribe Thus: ℞ Caps. Pituitary Co. (Harrower) No. C. Sig. One, q. i. d., a. c.

Price: Boxes of 100, $4.50.

Physiological Effects: Stimulates carbohydrate metabolism; increases cellular growth and encourages gonad function, especially in essential pituitary dysfunction.

Indications: The adiposo-genital syndrome of Froehlich; hypopituitarism; infantilism; eunuchoidism; maldevelopment of gonads (hypogonadism); developmental dystrophies of pituitary origin.

Remarks: Contains a greater proportion of the active glandular portion of the pituitary gland (the anterior lobe) than pituitary gland alone, hence is more useful in hypopituitarism, which is essentially an anterior lobe disease, than total gland products. Above figures refer to finished desiccated gland and not to fresh substance.

Reference: Sec. III, Part 1-B.

S. F. NO. 48. CAPS. PROSTATE COMP.

PROSTATIC DISEASE; Prostatic Neurasthenia; Hypertrophied Prostate; etc.

Formula: Each capsule contains six grains of the following combination. Prostate gland (desiccated), Spermin extract (from interstitial cells of Leydig) and Lymphatic glands, aa gr. 1½ Acid Nucleinic gr. ⅛ with Calcium Phosphorus Co. q. s.

Prescribe Thus: ℞ Caps. Prostate Co. (Harrower) No. C. Sig. One t. i. d. a. c. (Occasionally considerable increases in this dosage are helpful. It is also advisable to continue the treatment for several months, in which case I suggest its omission every fifth week.)

Price: Boxes of 100, $4.50.

Physiological Effects: Homostimulant to prostate and sex glands; antagonistic to prostatic irritability.

Indications: Latent prostatic insufficiency with or without an old posterior urethral or prostatic infection; prostatorrhea; endocrine insufficiency of the gonads with impotence, relative or actual. Prostatic hypertrophy. Prostatic neurasthenia and following prostatectomy. Senility.

Remarks: Of similar character to S. F. No. 70, Caps. Gonad Co. (q. v.)

Reference: Sec. V, Ch. 11 and 18.

S. F. NO. 49. CAPS. PLACENTA COMP.

VOMITING OF PREGNANCY; Nausea of Pregnancy; Placental Toxemia.

Formula: Each capsule contains six grains of the following combination: Placental parenchyma (desiccated) gr. 5, Thyroid gland (U. S. P.) gr. 1/24 with Calcium Phosphorus Co. q. s.

Prescribe Thus: ℞ Caps. Placenta Co. (Harrower) No. L. Sig. Contents of two capsules with charged water or ice, q. i. d.

Price: Boxes of 100, $4.50.

Physiological Effects: Antagonizes placental toxemia and sedates hyperemesis gravidarum. Presumed to act by artificially establishing an immunity to the placental protein poisons.

Indications: Vomiting and nausea of pregnancy.

Remarks: Often a last resort remedy of unusual efficacy when all other treatment has failed. Give by mouth with or without sedative medication. Morphine has been necessary to allow absorption. Give at times and under circumstances which will favor retention. Twenty-five grains a day for ten days, is usually a complete treatment since the expected results will come before this time if the measure is going to be efficacious. Continue for a longer time if evident benefit has been initiated.

Reference: Sec. III, Part 1-B.

S. F. NO. 57. CAPS. THYMUS-SPERMIN COMP.

ARTHRITIS; Arthritis Deformans; Chronic Rheumatism; Asthenia.

Formula: Each capsule contains six grains of the following combination: Adreno-Spermin Comp. (Stock Formula No. 1, q. v.) and Thymus gland aa gr. 3.

Prescribe Thus: ℞ Caps. Thymus-Spermin Co. (Harrower) No. C. Sig. One, q. i. d., p. c. (Occasionally given in larger doses for a few weeks, then reduced to the above.)

Price: Boxes of 100, $3.75.

Physiological Effects: Stimulates metabolism, antagonizes adrenal apathy and asthenia. (See No. 1. *Caps. Adreno-Spermin Co.*) According to Nathan and others desiccated thymus is effective in certain chronic arthrites, including arthritis deformans.

Indications: Chronic arthritis or rheumatism with poor metabolism and deficient cellular elimination. Arthritis deformans.

Remarks: Each of the ingredients of this formula, the Adreno-Spermin Co. and desiccated thymus have rendered service in arthritis deformans. In many cases the prospects for results are not bright, though this treatment has been used without hope

and as a last resort with results which were a pleasant surprise to all concerned. It must be given persistently. It may be well to modify the dosage by starting with the routine dosage suggested above, for a month, then omit one week and then take 2, q. i. d. for a month, then omit for a full month, then repeat this routine, taking note of any slight changes during these different periods. Only a part of the routine treatment.

S. F. NO. 68. CAPS. SPERMIN-HEMOGLOBIN COMP.

ASTHENIC ANEMIA; Hypoadrenia; Malnutrition.

Formula: Each capsule contains six grains of the following combination: Adreno-Spermin Comp. (Stock Formula No. 1, q. v.) and Repurified Hemoglobin, aa gr. 3.

Prescribe Thus: ℞ Caps. Spermin-Hemoglobin Co. (Harrower) No. C. Sig. One, q. i. d., a. c.

Price: Boxes of 100, $3.50.

Physiological Effects: Support to depleted adrenal function. Increases sympathetic tone, increases oxidation and "dynamos" (see Formula No. 1). Hematinic reconstructant.

Indications: Conditions of asthenia due to hypoadrenia with which anemia and malnutrition is present. Low blood pressure with anemia. Following operations and experiences which have depleted both the adrenal function and the blood.

Remarks: This formula is essentially the Adreno-Spermin formula to which attention has already been called, plus the effective hematinic, hemoglobin. *Caps. Spermin-Hemoglobin Co.* takes the place of the combined administration of No. 1 (*Caps. Adreno-Spermin Co.*) and No. 13 (*Caps. Hemoglobin Co.*), to which attention has already been called.

Reference: Sec. V, Ch. 9.

S. F. NO. 70. CAPS. GONAD COMP.

IMPOTENCE; Asexualism; Hypogonadism.

Formula: Each capsule contains six grains of the following combination: Adrenal gland (total) gr. ¼, Thyroid gland (U. S. P.) gr. 1/12, Pituitary gland (anterior lobe) gr. 1, Prostate gland and Spermin extract (from Leydig cells) aa gr. 1½ with Calcium Prosphorus Co. q. s.

Prescribe Thus: ℞ Caps. Gonad Co. (Harrower) No. C. Sig. One q. i. d., a. c. (Note: From 3 to 8 capsules may be given daily.)

Price: Boxes of 100, $4.75.

Physiological Effects: General cell stimulant, especially of the essential sex glands through the hypophysis, adrenals, thyroid and gonads themselves. The addition of the anterior pituitary

seems to be especially helpful (recall that the dystrophia adiposo-genitalis—hypopituitarism—is a functional genital disorder which has been benefited by suitable organotherapy). Antagonizes asthenia. Stimulates prostato-gonad function on the principle of homostimulation.

Indications: Functional and endocrine impotence; asexualism both organic and acquired; senility; presenility; hypogonadism; sexual neurasthenia; aspermia; sterility.

Remarks: Best given in step-ladder dosage, as 1, t.i.d. for several weeks, then 2, t.i.d. for a longer period, followed, if necessary, by another period when even 3, t.i.d. may be taken. Given in conjunction with associated treatment. Has no effect upon conditions with a psychic basis, nor does it influence latent infections. Not rapid in its action, therefore unusual caution must be taken to urge protracted use or not to start it.

Reference: Sec. V, Ch. 11 and 12.

S. F. NO. 73. CAPS. GONAD-OVARIAN COMP.

STERILITY; Hypoovarism; Asexualism; Infantilism; Amenorrhea.

Formula: Each capsule contains six grains of the following combination: Thyro-Ovarian Comp. (Stock Formula No. 4, q. v.) gr. 3, Spermin extract and Pituitary gland (anterior lobe) aa gr. 1½.

Prescribe Thus: ℞ Caps. Gonad-Ovarian Co. (Harrower) No. C. Sig. One q. i. d., a. c. If the patient is menstruating or there is a molimen, prescribe as formula No. 4, i. e., 1, t. i. d., a. c. for 10 days, double dose for 7 to 10 days before menses (or molimen), omit at onset of menses for a week. Repeat.

Price: Boxes of 100, $5.00.

Physiological Effects: Ovarian stimulant thru the endocrine function of the ovaries plus the gonado-stimulant effect of the anterior pituitary and the general sex and cell stimulant effect of spermin from the male gonads.

Indications: Prolonged amenorrhea; infantilism; sex maldevelopment and hypofunction; lack of libido; and, in general, the same as *Caps. Thyro-Ovarian Co.* (q. v.) save that the condition is more decisive and marked. Where the use of this latter has not been sufficiently stimulating enough.

Remarks: Endocrine stimulation thru all of the glands involved in "the sex complex" is about the only physiological hope in many cases of essential amenorrhea and sexual apathy in the woman. The cyclic method is better if it can be applied. Here, also, the gland feeding must be continued with persistence for long periods because the attempt is being made to re-educate certain endocrine functions, which naturally takes months and,

further, the time that the ovaries are especially stimulable only lasts a comparatively short time each month.

Reference: Sec. IV, Ch. 8; Sec. V, Ch. 3.

S. F. NO. 79. CAPS. ADRENO-OVARIAN COMP.

DYSOVARISM with Hypoadrenia.

Formula: Each capsule contains five grains of the following combination: Thyro-Ovarian Comp. with Adrenal gland (total) gr. ¼. (Colored for convenience in alternating with No. 4.)

Prescribe Thus: ℞ Caps. Adreno-Ovarian Co. (Harrower) No. C. Sig. One, t. i. d. for 10 days, double dose for 7 to 10 days before menses, omit at onset for 10 days. Repeat.

Price: Boxes of 100, $4.25.

Physiological Effects: Ovaro-uterine regulator thru the ovarian hormone function, plus adrenal support.

Indications: Ovarian dysfunction, amenorrhea, dysmenorrhea and, generally conditions in which the *Caps. Thyro-Ovarian Co.* would be used (see Formula No. 4) with hypoadrenia and asthenia, low blood pressure and general cellular apathy.

Remarks: Supplements the well-known Thyro-Ovarian formula with adrenal support and obviates the occasional necessity for prescribing *Caps. Adreno-Spermin Co.* with the ovarian treatment. Especially helpful in pallid, asthenic girls and young women with ovarian insufficiency, amenorrhea, etc. Also indicated in the climacteric when the dysovarism is complicated with an aggravated fatigue syndrome, etc.

Reference: Sec. V, Ch. 3.

S. F. NO. 82. CAPS. THYMUS-LYMPHATIC COMP.

LYMPHATISM; Adenoid Diathesis; Hypertrophied Tonsils; etc.

Formula: Each capsule contains five grains of the following combination: Lymphatic glands gr. 3, Pituitary gland (anterior lobe) and Thymus aa gr. 1.

Prescribe Thus: ℞ Caps. Thymus-Lymphatic Co. (Harrower) No. C. Sig. One, q. i. d., a. c.

Price: Boxes of 100, $3.75.

Physiological Effects: Alterative and reconstructant in lymphatic conditions; growth stimulant; endocrine regulator in certain types of children, especially with large and recurrent adenoids, hypertrophied tonsils, etc.

Indications: Adenoids, lymphatism and maldevelopment in children. (See also S. F. No. 43.)

Remarks: It has been stated that marked increases in adenoid and tonsillar tissue (especially at the usual age when this commonly occurs in children) may be a protective act on the part of the body, i. e., the organism was calling for greater service on the part of these lymphatic cells than they were able to supply. Suitable gland feeding has been claimed to reduce the size of such abnormal hypertrophy and thereby modify mouth breathing, snoring and the nutritional disorders of this class. In these cases, especially where the stature is small and development is slow, this formula may be given with hope of better results than the lymphatic feeding alone. It is being experimentally used with some encouragement.

S. F. NO. 85. CAPS. RENAL COMP.

NEPHRITIS; Albuminuria; Renal Insufficiency.

Formula: Each capsule contains five grains of the following combination: Desiccated renal glomerular tissue and desiccated pancreas gland, aa gr. 2½.

Prescribe Thus: ℞ Caps. Renal Co. (Harrower) No. C. Sig. One, q. i. d., a. c.

Price: Boxes of 100, $3.50.

Physiological Effects: Tends to reduce renal impermeability; lessens albumin elimination through the glomeruli; stimulates renal efficacy; encourages pancreatic and intestinal physiology.

Indications: Acute and chronic Bright's disease with or without albuminuria; essential albuminuria without other renal (or local) findings; deficient renal activity with polyuria and low total solids.

Remarks: For years renal glomerular substance has been recommended, especially in France, for nephritis and albuminuria. Various explanations have been given as to why it is useful, suffice it to say that many times it has reduced the urinary difficulties, both clinical and laboratory, of various forms of nephritis. The addition of pancreas gland is rational, for it tends to reduce the very conditions which are aggravating to the renal cells, as well as to neutralize the adrenal irritability so usual in such cases.

Reference: Sec. III, Part 1-B.

SECTION IV

THE DIAGNOSIS OF THE INTERNAL SECRETORY DISORDERS

There is no convenient source of information on this subject. Among the several books on endocrinology—notably Sajous, Biedl, Falta-Myers, Carnot and Pende—the whole subject is considered but largely from the standpoint of the well-defined, structural endocrine disorders. To my own way of thinking the functional endocrinopathies far outweigh the text-book diseases of this character, merely because they are so much more frequent, and so much more routinely overlooked.

This section contains a large amount of data on the diagnostics of endocrine disorders in general practice, *and is not intended to be either complete or technical, but rather to serve as a means of reminding the reader—presumably "an ordinary doctor" like myself—of some points which may be really helpful in the day's work.*

SECTION IV. CHAPTER 1

THE FREQUENCY OF INTERNAL SECRETORY DISORDERS IN GENERAL PRACTICE

The insidiousness and practical importance of disturbed function of the glands of internal secretion is far greater than most physicians realize; and the frequence with which it may be encountered in almost every phase of general as well as special practice, coupled with the fact that many times it is entirely overlooked, constitute the excuse for this section on endocrine diagnosis.

The Broad Influence of the Hormones. Increasing attention is being paid to the study of the glands of internal secretion, or endocrine organs, as we shall call them, and rightly so. Our knowledge of the physiological action of these organs has been acquired almost entirely in the last fifty years; and has been augmented very materially in the past 15 or 20 years. In fact practically all we know of the internal secretions has been learned in this brief period and the establishment of the fundamental contentions of the now famous French scientists, Claude Bernard

and Brown-Sequard, was not accomplished and their experiences scientifically explained until as recently as 1902, when Professor E. H. Starling, of University College, London, suggested the term "hormone" (from the Greek word which means "I arouse" or "I set in motion") to designate a class of chemical substances, of which his newly discovered secretin was the type (see Sec. V, Chap. 15), which are produced in various parts of the body and carried by the blood or other body fluids to various remote organs where they excite certain physiological manifestations, thus correlating the functions of numerous and widely separated organs.

The subject is of much more than academic importance for as an editorial writer in the *New York Medical Journal* (Feb. 26, 1916; p. 412) remarks: "Treatment based on the internal secretions, is in some instances, positively startling in its results, and bids fair to revolutionize our methods in several lines of practice; it is also eminently satisfying from a scientific viewpoint, being far removed from our old hesitating empiricism."

The endocrine glands, then, are factors of no mean import in the maintenance of that balance of activities which we usually call "health," and hence are worthy of more careful study and practical consideration in our clinical work. These organs and their hormones play a much more vital part than many physicians have allowed themselves to think. Variations in their activities deserve the closest attention, for too often endocrine disorder is only thought of when there is obvious disease of one or more of these glands. Since they are now definitely known to control growth and development, regulate metabolism and dominate the nervous system, more especially the sympathetic or autonomous system, their widespread activities assume a greater importance for it is quite clear that these hormones are altogether indispensable to the maintenance of the physiological harmony of the body.

The Minor Glandular Disorders. Too often we are prone to look upon this class of disorders as rare and occasional and their diagnosis as comparatively easy because of the obviousness of such well marked diseases as cretinism, myxedema, giantism or acromegaly. This is a mistake, for functional disorders of this class are of everyday occurrence and are naturally far more important than the more obvious organic diseases, for they are still in their earliest stages before serious disharmony has been caused; and, of course, are more responsive to suitable treatment.

Such all-essential factors in the regulation of human chemistry should be of interest to every general practitioner in his investigation of *every* condition in which disordered function is present. We should not be satisfied to know how to diagnose and treat those definite cases of definite endocrine disease, but rather

should we be always on the lookout to detect and understand the importance of the insignificant and minor aberrations from the normal, for in so doing in many a case we may be able to forestall the more serious and more obvious diseases which, if left alone, may later assert themselves.

As the larger functions of the internal secretions are being appreciated, their influence both for good and for bad is seen to extend far beyond the expected limits of definite endocrine disease, for as one writer has aptly put it: "There are a number and variety of conditions which can be understood and properly treated only after full comprehension of the work of the endocrine glands." All the uncounted clinical and experimental experiences which have been directed towards the solution of the numerous problems which this ever-broadening subject has opened up, have convincingly demonstrated that the influence of the various units of the endocrine system, as well as of the body as a whole, is far more extensive and complex than even the best posted physiologists had supposed, and that many phenomena credited to nervous or sympathetic nervous influences were really the result of hormonic disharmony. In fact we know as a result of the painstaking work of Cannon, Crile, Elliott and Sergent, that as the sympathetic system is under the direct control of one or more of these hormone influences, disorders with prominent sympathetic disturbances, as shock, collapse, hysteria and other neuroses, may be traced further back than we have been in the habit of doing heretofore and, what is of far greater practical importance, may be controlled by applying the principles which the study of this subject simultaneously has proved possible in the domain of therapeutics. Crile's exhaustive study of the kinetic system—the adrenals, thyroid, brain and muscles—and its practical application in what he chooses to call "anoci-association," is but one of many profitable phases of this huge subject.

Broadening the Therapeutic Horizon. Now that the interest of the aggressive section of the profession is being focussed upon these glands, and much regarding their study and the importance of the many phases of the subject is appearing in current medical literature, a comparatively new branch of medicine is gradually being differentiated, and with the better knowledge that we have of the physiology of the hormone-producing organs, there comes not merely an increased diagnostic skill, but a broadened therapeutic horizon, *for in the study of the internal secretions lies the future of the treatment of most functional disorders.* To tell the truth the extensive ramifications of this subject and the increasing prominence of the endocrine features in so many minor as well as important disorders, is awakening an interest in the new specialty. As Sajous says, this branch of medicine "claims the right to exist as a specialty for

its field is greater in scope than some which have earned well merited recognition." ("Hemadenology: A New Specialty," *N. Y. Med. Jour.*, Feb. 20, 1915, p. 365.) Sajous then continues: "Its influence on the improvement of the race through the light it will shed upon the pathology of the unfit, mental and physical, cannot but prove a blessing. If to this we add the many disorders it will serve to elucidate through collective effort on the part of the host of investigators it is bound to enlist . . . the day may come when the inauguration of hemadenology may be considered as having marked a new epoch in medicine."

All who have studied this subject admit that it has a fascination that cannot be measured. The profitable applications that have been made in clinical practice by the employment of organotherapy, or "hormone therapy," explain in a good measure the favor with which this subject is being received by the medical world.

As we occupy ourselves in searching for the earliest signs of endocrine disorder, automatically we gain a better insight into the intricacies of the functions of the body and are not merely able to forestall the later and more serious organic disease, but so often we run across associated manifestations of the most diversified kinds, from nocturnal enuresis to chilblains or from neurasthenia to a stiff neck, which may be modified directly by suitable organotherapeutic measures which we may be directing at an associated but entirely different condition.

What Some Authorities Have Said. None can deny that a knowledge of these twin subjects—endocrinology and organotherapy—has put an entirely new aspect on the outcome of many intractable disorders. The increasing appreciation of the role of the endocrine glands has, as Leonard Williams has said, "lightened our darkness and shown us miracles." What other word than "miracle" can be applied to the startling effects of thyroid feeding upon the pitiful conditions of cretinism? How many of the "darknesses" of practical medicine are being illuminated by what science has taught us regarding the hormones in physiology and therapeutics, will be more evident as the reader finds opportunity to apply this knowledge in his daily routine.

In the words of an editorial writer in *American Medicine:* "Many a chronic and intractable disorder is due to an overlooked defect in the production of the hormones of the internal secretory glands. Increasingly greater stress is being laid upon the importance of these chemical messengers, and there is now little doubt that in health as well as in disease they regulate and correlate the metabolic activities of the body." Again the importance of this is emphasized in a recent review in the *Lancet* from which we quote: "As our knowledge has progressed, the influence of the ductless glandular system has proved to be far wider and more penetrating than any of the earlier investigators

suspected. It controls growth and metabolism and in short, determines largely the nature of that factor which the older physicians spoke of as 'constitution.'"

The internal secretions have revolutionized physiology and with it clinical medicine, just as organotherapy has revolutionized certain phases of treatment; hence the general practitioner, above all others, stands to benefit by this added fund of knowledge. As we become better acquainted with the endocrine disorders it will be noticed that intimations of their presence are staring at us in every turn in our daily routine; and we will find many an occasion to congratulate ourselves that we have taken time to investigate this fascinating and interesting subject.

SECTION IV. CHAPTER 2

THE MINOR THYROID DISORDERS

A full appreciation of the clinical importance of the disorders of the thyroid gland presupposes a knowledge of the essential role that it plays in the regulation of the functions of the body. Truly it is a most wonderful organ, and it has been called very aptly "the keystone of the endocrine arch."

The Director of Metabolism. As such it is the most important single factor in the direction of the intricate workings of metabolism, for it has been well affirmed that the thyroid governs growth and development—physical and mental, controls the breaking down of certain food materials, particularly albumen, and has much to do with the regulation of the complex chemical processes by means of which the cellular wastes are disposed of. As a consequence of this many different physiological manifestations are intimately bound up with the work of the thyroid and its functional disorders, no matter how slight, are immediately reflected in such functions as heat regulation, muscular efficiency, peristalsis, urinary excretion especially the elimination of nitrogen, menstruation and other activities of the gonads (essential sex glands), both in the male as well as the female, the different features of mental capacity, hematopoiesis, nutrition especially of the skin and its appendages, as well as the development of features, form and function generally.

The thyroid hormone also has to do with the powers of the body to resist disease. Sajous was among the earliest to connect its work with the production of immunity, and it has been shown to be the most important of the numerous detoxicating agencies at work in the body. This last makes the thyroid especially susceptible to the toxemias associated with the infectious

diseases and the infections, in fact the chief causes of thyroid insufficiency—the minor and by far the most frequent form especially—are the infectious diseases, principally tuberculosis, syphilis and the exanthemata and, of course, typhoid, diphtheria, rheumatic fever, influenza, erysipelas and many other acute or chronic focal infections.

The Relation to the Sex Glands. The predominating influence of the thyroid upon the functions of the gonads renders it peculiarly sensitive to variations in the sexual life, especially in women; and emotional or sexual excess, as well as the toxic and functional disorders associated with pregnancy are frequent causes of the slighter forms of thyroid insufficiency. On the other hand the sex hormones react upon the thyroid, and thyroid dysfunction is a common result of disturbed gonad function, especially of the ovaries. Incidentally this lends emphasis to one of the difficulties of endocrine diagnosis—both thyroid and ovaries react upon one another and it is sometimes difficult to know whether a given condition is causative or resultant.

The intimate relation of the thyroid to metabolism, particularly that of proteids, makes it react to that unfortunately all too common etiologic factor in so many disorders—overfeeding, and this is particularly true of a diet in which meat forms a generous part. Intoxications of all kinds—intestinal, alcoholic, drug and those due to ameba in the mouth or tonsils and to intestinal and other parasites—are not infrequent exciting causes of a breakdown in the thyroid function.

With the foregoing suggestions in mind, coupled with the fundamental physiological fact that the thyroid is as important a factor as any in the detoxicating and immunizing processes of the body, it will be clear that the detection of a minor functional disorder of this gland may be of much more service than merely to direct attention to the measures necessary to reinforce the work of the lagging gland. A much more important thing will have been accomplished if, in addition to this, the underlying causative element is laid bare and steps taken to eradicate it or to nullify its influence. Very, very often the proper adjuvant treatment of thyroid inadequacy—the treatment of its cause as well as its results—is made possible by applying our increased knowledge in the right way. Hence we would naturally supplement thyroid medication with emetine where alveolar or tonsillar amebiasis is present whether the infection has made itself prominent or not. Bacterial vaccines would be administered where there is a definite underlying bacterial origin, autogenous vaccines where cultures may be made easily, or, better still, mixed stock vaccines, especially where it is difficult to locate the nidus of infection and secure a culture. Again systemic alkalinization or remineralization, as the French usually call it, (see Sec. V, Chap. 16) is very much in order where acidosis and toxemia

are prominent; in fact in almost every case of chronic benign thyroid insufficiency, generous and judiciously timed doses of the alkalies, preferably in proportions similar to those found in the blood, will make the response to thyroid therapy much more satisfactory. Where intestinal concretions are palpable and stasis is obvious, eliminant and lubricating remedies facilitate the best results by removing the wastes which not merely aggravate the manifestations of thyroid disorder, but hinder every function of the body.

For these reasons, then, I rarely employ thyroid medication without some associated treatment, and am confident that many a failure in this line of therapeutic effort is due to the omission of the necessary adjunct measures; for many a time it will be found that a certain method of treatment is rendered much more efficient by the addition of thyroid (say ¼ or ½ a grain three times a day), while the reverse is equally true—thyroid therapy is enhanced by combining with it other suitable treatment the need for which is too often overlooked.

Before we pass from the consideration of the underlying basis of thyroid disorder a word of emphasis may be advantageously placed right here. Has it ever occurred to the reader that one of the commonest features of the heavy eater or drinker is obesity, and that this is also a common and quite constant feature of hypothyroidism? Why should the thyroid glands of those who are wont to abuse their bodies be so immune to the influence of the very factors which most commonly disturb their function? They are not, and an almost constant feature of such individuals is hypothyroidism manifested in not a few disorders other than the one just mentioned, of which we shall shortly learn. It is fair to add that these factors just mentioned are not the only causes of the thyroid type of obesity, for in some cases the cause cannot be established.

The Predisposing Causes of Thyroid Instability. All these exciting factors, and others quite similar to them, are clearly much more effectual disturbers of the chemical routine of the thyroid gland when the individual has an unstable thyroid mechanism to start with; and as with the major thyroid diseases, about which we shall have more to say later, heredity is the one great foundation upon which a susceptibility to thyroid dyscrasia is built. This is the great predisposing cause while the toxemias and other circumstances previously mentioned are the principal exciting causes.

Many conditions combine to favor the production of congenitally subthyroidic children, most important among which are various degrees of the same disorder in the parents and especially the mother. Transmitted tendencies toward tuberculosis, malnutrition and other congenital ills to which the flesh is all too often heir, not forgetting inherited syphilis—a most potent cause

of every kind of functional and organic disease of the glands of internal secretion—are almost invariably associated with thyroid instability, and by this is meant, not necessarily definite thyroid disease of varying degree, but an inherent cellular weakness of the gland which permits it to succumb to the first serious stress that may be put upon it.

Usually this extra strain may be the result of some of the common infectious diseases of childhood (incidentally children with this unstable condition are just the ones who "catch everything") or it may not appear until puberty, at which period many a thyroid insufficiency of more or less permanency first makes itself manifest either by structural changes, as goiter or but the disturbances which result from hypothyroidism.

Other factors which favor the hereditary subthyroidism in children are toxemias during pregnancy and labor prior to their birth. I have frequently found a connecting thread between such conditions and the complex endocrine disorders which I so often see, and it would be interesting to see a report of the thyroid findings in a goodly number of individuals whose advent into the world was the occasion of eclampsia, some figures which I do not believe have yet crept into medical literature. Important among the other predisposing hereditary causes of thyroid instability are unduly frequent childbearing, prolonged lactation and other physical strains upon the system of the mother during pregnancy. Acute infectious diseases of the mother may cause this tendency in her offspring; though it should be said with emphasis that these conditions just mentioned do not necessarily spell thyroid inadequacy in the child and, of course, a constitution may be acquired after birth and in spite of a poor hereditary.

Perhaps additional emphasis should be given to the importance of syphilis as a predisposing as well as an exciting factor in this class of cases. We are taught to consider syphilis as a prospective cause of every obscure and difficult condition and to presume its presence until it is definitely ruled out. This is the correct though not the usual way to look at the subject. The advent of the Wassermann test and its standardization and control by other procedures has made it possible to know with definiteness whether the syphilitic factor is present or not, and every insidious case of this character should have the benefit of the Wassermann test at least of the blood, and not infrequently of the spinal fluid also.

Syphilis is the most insidious of all diseases and is most protean in its manifestations, and Dr. L. F. Barker, of Johns Hopkins, was right when he recently told the New York Academy of Medicine that "the more my experience grows, the more I am inclined to take as a diagnostic aphorism, 'When in doubt have a Wassermann test made; when not in doubt still have a Wassermann test made.'" And in no class of disorders, is this

more truly applicable than the obscure and insidious, just like the obvious and organic, diseases of the glands of internal secretion.

Having attempted to direct attention to the numerous contributory causes of thyroid dyscrasias, as well as to the factors which are likely to precipitate slight or well marked thyroid insufficiency, we can now more intelligently proceed to consider the clinical results of this condition, and to the study of how to detect the usual and unusual symptoms of this common disorder.

From what has been said regarding the exciting and predisposing causes of thyroid disorder, it will be clear that the history, both personal and family, is particularly important as in it we may find a strong hint as to the prospective presence of the condition for which we are looking, although we may not always find a basic reason of this character in our anamnesis, for thyroid disturbances have a habit of appearing without the necessary hereditary or even the presumably essential etiologic foundation.

Hypothyroidism may be found at any time during life, from infancy to old age, though it is most common in young persons. The more serious forms are likely to show themselves in infancy or youth, while the forms that are usually overlooked altogether are more usual during the thirty or more years of active reproductive life and, as has been mentioned, it is especially frequent in women.

Infiltration, the Chief Symptom of Hypothyroidism. When we recall the principal intra-cellular functions of the thyroid hormone, it will be easy to understand that aberrations in the production of this chemical messenger not only interfere with cellular growth, but they derange the essential chemical changes connected with the incessant regeneration of the cells themselves. Their waste products are retained and the effete material is not burned up, facts which are proved in several different ways. The chief result of this special form of suboxidation is the establishment of a condition of *cellular infiltration* which varies both in degree and in the number and location of the organs attacked. That it is often generalized cannot be denied, but that it is more manifest in some tissues is also true, as we shall see when the results of the more serious forms of thyroid disease are considered.

While the loss of the normal thyroid stimuli may account for many disorders, more clinical symptoms result from this infiltration than from any other single result of thyroid derangement. As we enumerate the symptoms of thyroid disorder this one factor—infiltration—stands out above all the others, and when its importance and extent, as well as the fundamental philosophy of its presence, is thoroughly understood, it will explain many a symptom which previously had not been supposed to have the least to do with this gland. The credit for the discovery and

announcement of this phenomenon undoubtedly belongs to my good friend Dr. Eugene Hertoghe, of Antwerp; and to him is due the homage of the medical profession for his remarkable contributions on this subject. The importance of the whole subject may be impressed by a quotation from a recent paper ("Thyroid Insufficiency," *Practitioner,* Jan., 1915, p. 27) by this eminent authority. "It is obvious that myxedematous dwarfism and infantile cretinism cannot escape detection by a physician of even moderate attainments . . . but the slighter forms of thyroid inadequacy are almost invariably missed; yet, owing to their extreme prevalence, the recognition of these is extremely important"—although more than twenty years have passed since the symptomatology of "chronic benign thyroid insufficiency" or *"myxedeme fruste"* was first described.

This is just as true of the other functional endocrine disorders, and the fact that they are so very often overlooked, and information as to how to detect them is not easy to obtain, is, it is to be hoped, a sufficiently good reason for the emphasis which is being laid on the subject here.

The Frequency of Hypothyroidism. Thyroid insufficiencies are more frequent than the exanthemata. Minor hypothyroidism is among the commonest of disorders. It complicates pediatric problems more often than almost any other single condition except, of course, disorders of infective origin. It is equally important in the etiology of many functional gynecological troubles as well as in many of the complexities of internal medicine. Neurologists are now coming to consider it as a much more vital factor in their difficult cases than has previously been supposed and it may be considered to be an insidious complicating element in many chronic diseases including that symptom-complex usually called "neurasthenia" for the lack of a better name.

Close study is always rewarded by results which usually have a very definite clinical significance. This is as true in endocrinology as elsewhere; and to the seeing eye is unfolded many an obscure condition of daily occurrence. These are obscure merely because their insidious onset hides them. They have not been looked for. The secret of success in endocrinology is thoroughness. It is the little things that count; and it is surprising how the appreciation of a seemingly insignificant circumstance enables us to correlate some other equally insignificant condition, and thus to pass the unseen barrier which has been separating us from a full understanding of a given case.

The processes of cell-exchange, nutritional and eliminative, influence all parts of the body, hence, as Hertoghe puts it: "No tissue is able to escape the results of impoverishment of the thyroid gland." These results are just as real and important from a practical standpoint as many other obscure but none the

less important disorders. They are often even more important, for their very obscurity means that their discovery may be of unusual helpfulness. The fact that they have been overlooked has made a great difference to the treatment and accounts for many failures; and their discovery may put an entirely new aspect upon the prognosis, for the treatment of internal secretory disorders with well marked and organic involvement is not always as successful as that of those conditions in which only the early, functional changes are beginning.

Principal Results of Thyroid Insufficiency. So many organs and systems may be affected by disturbed thyroid secretion that it is necessary to consider separately the principal changes in the different tissues. It should be remarked, however, that not all of the conditions shortly to be enumerated will be found together in a given case, not even in the serious form of hypothyroidism. The detection of several of them is sufficient ground for the application of suitable thyroid therapy. This is not empirical thyroid medication, for further proof of its scientific basis is forthcoming when the response is favorable, for Hertoghe's statement must be taken as axiomatic that "those who derive benefit from thyroid medication invariably will be found to show symptoms of thyroid inadequacy"; and if thyroid may have been indiscriminately administered—a not infrequent happening—and the results are favorable, this may be taken as a therapeutic-diagnostic test* (just as certain treatment was the only definite way to demonstrate the etiology of certain brain tumors, a procedure which is now entirely superseded by the Wassermann reaction).. The most common example of this is the response of some obese individuals to empirical thyroid medication.

As the thyroid plays such an important part in so many of the activities of the body, its functional derangement may result in the commonest of pathological conditions. Inadequate or suppressed thyroid function causes morbid syndromes in direct ratio to the loss of the thyroid hormone to the body; and this may affect almost every tissue and function. Perhaps the most common and constant changes resulting from hypothyroidism are seen in the skin and its appendages. It is infiltrated with waste products, puffy and insufficiently nourished so that it becomes dry, rough and desquamating. Sensible perspiration is reduced and in advanced cases not even exertion in summer heat will awaken the dormant sweat glands. Usually the more marked edema is only present in myxedema which will be considered later. Many dermatoses may be found. In children eczema is most common; at puberty, especially in girls, acne and

* Elsewhere a method of testing thyroid function is outlined. It is really a routine, uniform application of the principle just mentioned.

in adults herpes, psoriasis, urticaria and dermal malnutrition and susceptibility to slight cutaneous infections with varying symptoms. According to Leopold Levi subthyroidism provides a favorable soil for recurrent erysipelas and he has found that this condition has yielded readily to thyroid.

As a result of the infiltration the hair is sparse, thin and ill nourished, falls out easily and characteristic of certain stages of this condition is the "signe du sourcil"—a commencing or absolute loss of the outer third of the eyebrows. For the same fundamental reason the nails are often striated and brittle, later cracking very easily. The teeth are bad, caries being a common result of hypothyroidism, and a routine finding in children with thyroid defects. In fact the child with bad teeth should be studied from this particular viewpoint, and very frequently other prominent results of the underlying hypothyroidism are discovered; and the obvious treatment will be most helpful besides local dental care.

The generally deficient cell oxidation commonly results in the temperature being below normal, and occasionally it is lower in the late afternoon at which time there may be fits of shivering, at times simulating malaria very much. There is a general chilliness and the extremities are cold. These individuals feel the cold very much and require undue amounts of clothing or bed coverings. They are continually complaining about the cold, take all sorts of precautions to guard against it and slight draughts cause rheumatoid or neuralgic pains. "Dead fingers" are often due to this cause and cyanosis and even chilblains are connected by many authorities with hypothyroidism. Raynaud's symmetrical gangrene and other forms of vasomotor spasm with skin manifestations are also credited to the same fundamental cause; and time and again have disappeared when suitable needed treatment is instituted.

Fatigue, especially in the morning, is usual. Subjects of this disorder were "born tired" and require much sleep. The cellular apathy causes them to sleep very heavily, often in the day, especially after eating. There is a feeling of depression and well-marked cases are apathetic, disinterested and "lazy."

The infiltration and generally devitalized condition naturally favors obesity. The muscles, joints and ligaments are all similarly influenced, producing such common symptoms as "rheumatism," stiff neck, aching in the limbs and back often especially marked between the scapulae. The joints may be stiff and occasional swelling may suggest arthritis and even ankylosis. Cracking noises in the joints is not unusual and Hertoghe speaks of it being very common in the knees. The involuntary muscles are also affected, the intestinal and abdominal walls are weak and ptosis is the rule. Stasis, constipation and the accompanying toxemia complete a vicious circle. Many of the symptoms

so widely emphasized by Sir Arbuthnot Lane were connected and described by Hertoghe 15 years before and definitely credited to "benign chronic subthyroidism." (See E. Hertoghe, *Bull. Acad. Med. de Belg.* March, 1899, p. 231.) For many years he has successfully treated such cases on this basis, and while there may be an advantage in the present vogue of intestinal lubrication and, rarely, even in the operative measures recommended, the elucidation of the fundamental cause and its removal is a much more satisfying as well as rational procedure. Obstipation of the most aggravating type is not uncommon. The stools are hard because of the decreased alimentary secretion. The appetite may be progressively poor and certain foods, especially meat, are intensely disliked. The appearance is toxic and often prematurely senile and in advanced cases a brownish pigmentation of the skin, commonly more marked on the exposed portions, has been remarked by some writers.

A sensation of heaviness over the epigastrium is not unusual and biliary colic has been caused by infiltration and nothing else; and nutrition is below par, though the weight may be normal or, more often, increased. There is a reduction in weight when our therapeutic efforts begin to relieve the infiltrated cells throughout the body of their accumulated wastes. Hertoghe uses the term "thyroid inanition" which refers to a condition of cell starvation, inactivity and asthenia without obvious changes in contour or weight. Vomiting, in some cases, may be due to this same fundamental cause, especially when associated with pregnancy.

The infiltration does not miss the cardiac muscle and in consequence the heart action is weak and the pulse usually slower than normal. Circulation is especially poor, accounting for some of the manifestations (associated with the infiltration) just connected with hypothermia. Respiratory oppression and varying degrees of dyspnea are frequent. Occasionally this is intermittent and mistaken for asthma, thus explaining the occasional unexpected cures in "asthma" following thyroid therapy. According to Hertoghe "the physiologic stimulant of the heart is supplied by the thyroid. It is, in a certain sense, the necessary tonic, the normal digitalis, by which cardiac activity is promoted and maintained. . . . I do not hesitate to exhibit thyroid extract in cases of weak contractility and tendency to syncope, and I may say that the treatment has never failed me." (See article mentioned above.)

The desquamation so marked on the epidermis, as well as the infiltration and loss of function due to it, is also present in the bladder which, by the way, seems to be peculiarly supersensitive in hypothyroidism. An excess of squamous cells is common among the urinary findings, and the incessant denudation results in an undue sensitiveness to contact with the urine, causing fre-

quent urination and enuresis, especially in children who, it will be remembered, are very heavy sleepers (with consequent decreased control over the ejaculator urinae reflex) as a result of which bed wetting is not unusual. The other urinary findings show the reduced oxidation very plainly. This is especially noticeable in the low urea output. In such cases there is often a tendency to acidosis and an estimation of the ammonia will show that generally it is unduly increased, due to the imperfect metabolism in the liver of the "urea precursors." It almost seems that there is a distinct connection between the thyroid and the liver, for in the more marked cases of hypothyroidism, not only are the chemical functions of the liver disturbed, but it becomes infiltrated, passively congested and tender on pressure. The same is true of the gall bladder and the desquamation there favors the production of gall stones or jaundice with their usual symptoms.

The mental disturbances are many and varied. Slowness characterizes every form of mental action. The memory becomes gradually poor, there is difficulty in following a line of thought or reasoning. Apathy, somnolence and melancholia and in the more marked cases organic brain disorders with varying forms of mental deficiency may be present. Headache is a usual and early symptom, especially when it occurs early in the day. It is so constant in some cases that they have accustomed themselves to it, and "have it all the time." Neuralgia and migraine have been definitely traced to the thyroid and the conclusions verified by the therapeutic test. Two insidious subjective symptoms may be present which are rarely thought of in connection with this disorder. These are giddiness and noises in the ear. The generalized infiltration is again responsible, and the same thing also may cause hoarseness, a change in the timbre of the voice, and even aphonia.

The effects of thyroid dyscrasia on the gonads are well marked and among the most constant findings, especially in women. Early thyroid disorder spells late reproductive activity. Often the menses are delayed for years, or after having started may be suppressed for a varying period. Amenorrhea is sometimes noticed, especially in young girls; but in women, especially towards the close of reproductive activity, when the characteristic infiltration is present the reverse is the rule, menorrhagia, severe and persistent, is a common result. It is believed by some that the thyroid has something to do with the development of the uterus, and that when hypothyroidism is fairly well marked the posterior uterine wall is not properly developed, sometimes causing a marked retroflexion which may be a part of the cause of the menorrhagia. The menses are prolonged, may recommence after they are apparently over, the frequency of the periods is increased and the loss of strength and activity is especially

noticeable. "The higher the degree of thyroid inadequacy, the greater the menstrual losses" (Hertoghe).

Many a case of severe dysmenorrhea has an important thyroid element in its causation, and this factor may outweigh all the other associated conditions. These cases nearly always show one or more of the other symptoms of thyroid inadequacy, and the success of thyroid or thyro-ovarian therapy (E. Hertoghe, *Practitioner,* Jan., 1915), will be the best proof of the correctness of our surmises.

The "Classic Picture" of Hypothyroidism. I have enumerated many symptoms referable to thyroid insufficiency, so many, in fact, that a catalogue of the possible symptoms of this disorder render the cataloguer open to ridicule! The fact remains that they may all occur as a result of this disorder though we may not find more than three or four of these signs in one case. However, it is by no means uncommon to find an individual showing what might be called "a classic picture" of hypothyroidism—severe headaches, neuralgia, "rheumatism," constipation, ptosis, skin disorders, hypothermia, chilliness or distinct chills, slight dyspnea perhaps better referred to as a sense of undue oppression on the slightest effort, asthenia, mental changes of a minor character as loss of memory, inability to concentrate, menstrual disturbances, etc., etc.

Such cases, heretofore an unmitigated nuisance, both to their relatives and their physicians—for too often they have perambulated from one physician's office to another—may now be considered as of unusual profit, for their treatment by attention to the necessary hygienic measures plus thyroid therapy very often means results, the like of which cannot be obtained in any other manner. Such patients are amazed at their progress, their friends see changes in their features and their "view of life" that makes for success in practice.

Let us not allow the slightest phase of minor thyroid disorder to pass us again; and let us always remember that if our diagnosis is wrong the treatment will show it!

SECTION IV. CHAPTER 3

THE MORE SERIOUS ORGANIC THYROID DISEASES

Like most organs of the body, the thyroid gland may be the subject of both hypertrophic and degenerative diseases. These exert a well marked influence upon the physiological activities

of the organism, not merely due to the effects of the disease *per se,* but more particularly because of the widespread effects of the resulting dyshormonism.

Thyroid Tumors—Goiter. The thyroid gland is commonly the seat of changes which result in the production of tumors, and while the organic disorders such as carcinoma and sarcoma are somewhat rarely found in this gland, it is considerably more frequently modified by a tumor growth known as an adenoma, which may or may not become malignant. It should be understood that these tumors may be present with no decided change in the internal secretory capacity of the gland, while on the other hand either a reduced or an increased functional activity may accompany the evolution of the new growth. This change in endocrine capacity may be determined by my Thyroid Function Test. (See Chapter 4 of this Section.)

Quite the most common tumors of the thyroid gland are the well known goiters, the incidence and frequency of which is well recognized, and the symptoms of which may vary from the seriously toxic exophthalmic form of goiter to the practically inactive hyperplastic condition. It is very necessary to be able to differentiate between the various forms of thyroid enlargement, since both prognosis and therapeutics depend altogether upon the variety of pathological change that may be present. It must be remembered that at the beginning of puberty and during pregnancy, there is a normal functional increase in the work of the thyroid and frequently this is accompanied by a slight enlargement of the gland which has no pathological significance. These physiological enlargements should be watched, however, as the change from normal to abnormal is insidious and, unfortunately, quite common.

The so-called "simple goiter" may be of three distinct types: (a) Parenchymatous (increased proliferation of the thyroid structure and follicles) in which case the gland is moderately firm to the touch and regular in form; (b) colloid (increased production of the material in the follicles) with a comparatively large and soft tumor; and (c) cystic (a modification similar to the colloid form in which the follicular contents are fluid) in which there is a distant fluctuation present.

With these several forms of simple goiter there are often no important general symptoms, although one must expect to find local disturbances depending upon the degree of pressure that may be exerted by the enlarged gland. It can be readily understood that the intrathyroid changes may diminish the secretory powers of the glandular tissue, whilst the hyperplasia causes a considerable increase in the size of the gland. This explains the presence of hypothyroidism in goiter and also the occasional value of thyroid therapy in goiter, for as Falta says: "For the most part there is sufficient parenchyma capable of functionating."

When this comparatively healthy portion of the gland is not enough to supply the necessary amount of hormones, the homostimulant action of the thyroid which may be administered, suffices to increase the functional activity of the healthy remainders and thus augment the deficiency with resulting clinical benefit.

The "simple" goiters may and quite frequently do lose their simplicity—the sound secretory portions of the gland may hypertrophy and a condition of hypersecretion supervene—in which event the clinical diagnosis is not usually made by the local examination, but rather by the study of the manifestations of dyshormonism which accompany the goiter, and which will be referred to shortly.

The well defined and localized goiters, or adenomata commonly have a distinctly nodular feeling. Where there is an accompanying syndrome which includes anemia and cachexia, suspicions of malignancy are warranted. The confirmation of such suspicions is usually made after an operation, although occasionally the presence of metastatic growths is convincing though belated evidence of the malignant character of the tumor.

The thyroid gland may be the subject of an acute infectious process of varying severity. This has been seen to follow an infective process elsewhere in the body, particularly in the tonsils, as well as a number of the acute infectious diseases. Not infrequently it occurs in the primary stage of syphilis. From a diagnostic standpoint the most important findings in acute thyroiditis include the rapid onset and well defined enlargement of the gland with extreme local tenderness, exquisite pain extending up and out to the throat, ears and neck, fever, the results of increased thyroid function—especially cardiac, and, in advanced cases, pus formation with fluctuation.

Sclerotic changes may follow an acute inflammatory process and are not uncommonly also seen in tuberculosis, syphilis and alcoholism. The direct result of this condition is likely to be a varying degree of hypothyroidism (discussed in the previous chapter) which in the course of time even may become a well defined myxedema.

Myxedema. The organic changes in the thyroid just mentioned are less frequent than these functional-organic changes which differ from the minor thyroid disorders already outlined, only in degree. The well defined and chronic secretory disturbances of the thyroid gland are practically always accompanied by structural changes, insufficiency being associated with sclerosis or atrophy (though as we have seen, goiter is commonly accompanied by hypothyroidism) and increased activity with hypertrophy and increased vascular engorgement.

The first of these is myxedema or organic hypothyroidism. We have already seen that this may be of very slight degree with a large series of inconspicuous symptoms. It may be more

marked—the *"myxedeme fruste"* of Hertoghe, or, again, it may be so well established that the thyroid aplasia results in a typical myxedema, the symptomatology of which we now may discuss briefly. Incidentally the disorder known as cretinism is really an early myxedema or athyroidia, and save for the well defined development disturbances due to the earlier lack of the thyroid hormones, the symptoms are practically the same.

Naturally one would expect to find a similarity between the manifestations of myxedema and the minor form of hypothyroidism, and this is the case, the difference being chiefly in degree. The changes in the skin are most obvious and it is due to their prominence that the disease received its name. They are dependent upon the condition of infiltration or edema (which is not really edema, for the infiltrated products are mucoid rather than fluid and there is no pitting on pressure), which causes well marked trophic changes in the skin itself, as well as in the dermal appendages. The color of the skin is a buff-pink, sometimes almost grayish. It is said by some to look like alabaster. It is puffy, dry, desquamates easily, and the sweat glands are inactive. The skin is often unusually susceptible to local infections. The hair is dry and brittle and falls out in large quantities. The nails crack easily and are dry and poorly nourished. The teeth are almost invariably in very bad order.

The vital processes as a whole are reduced to a minimum. The temperature is from one to several degrees below normal, metabolism is reduced and with it the elimination of wastes by all channels. Toxemia is, therefore, the rule and this favors a condition of invincible constipation which is also usually present. Despite this toxemia the heart action is usually reduced with a slow pulse and a tension often much below normal, due to the associated adrenal insufficiency which will be considered in another chapter. As a further result of this there is a well marked anemia and especially a hemoglobinemia.

The retrograde changes in the mental powers are very marked, in fact the whole of the nervous system is extremely inactive. The reaction of the body to external stimuli is very poor. Mentality may vary from dullness to complete amentia, and in early cases, loss of memory and inability to concentrate and the general disinclination to use the mental powers is the rule.

Impotence is the rule in men, and in women either amenorrhea or menorrhagia. (In the first instance the gonads lack the stimuli from the thyroid which are undoubtedly a factor in establishing and maintaining the molimena, while in the latter the infiltration of the myometrium and endometrium coupled with a subtle change in the chemistry of the blood may cause an increased and prolonged menstrual flow.) Atrophy of the genitalia may take place, but is not so marked as in pituitary disease, of which more later.

Cretinism. In infantile myxedema or sporadic cretinism, in addition to the findings previously mentioned, there is an almost entirely retarded mentality and physical backwardness and, of course, the sexual development is practically stopped. The face has a broad, puffy, "sloppy" appearance, the "saddle nose" is frequent, and the capacity to respond by a smile, a twinkle of the eye, or motions of the facial muscles, is almost entirely lost—but this is mental, as suitable tests will show no paralysis present. The mouth hangs open, the lips are large and the teeth are delayed in their eruption, and when seen are carious and widely spaced. The bones are abnormally formed, short and stubby. The figure is deformed, the gait awkward, and sometimes walking is impossible. Coordination is poor. The abdomen is soft and prolapsed, the condition known as "pot-belly" being frequent. The cretin does not grow up and the mental and physical stigmata just mentioned above, and illustrated in practically all books on the subject, make a pitiable picture.

The general metabolic inactivity favors the deposit of fat and the condition of thyroid obesity is quite common in cretinism as in the minor hypothyroid insufficiencies.

A word should be added here about "endemic" cretinism as compared with the "sporadic" form just mentioned. This condition is extremely rare in the United States, but common in Switzerland and Austria. The distinction lies in the heredity: endemic cretins are descended from cretin families and are born in places where cretinism is prevalent. The clinical manifestations are, perhaps, not always so completely typical as in the sporadic form, and occasionally procreation is possible. In addition to the stigmata of cretinism already outlined, umbilical hernia is very common in the endemic form of cretinism. Deaf-mutism is very often associated with thyroid aplasia. According to Scholz nearly 30 per cent. of the endemic cretins seen by him were deaf mutes.

There is another important distinction between these two forms of cretinism—the sporadic form responds wonderfully to thyroid medication, while the endemic form may or may not be benefited by this method of treatment.

Hyperthyroidism. The other principal form of thyroid dyscrasia is thyrotoxicosis or hyperthyroidism, and is the best known and most complex of all the functional thyroid diseases. Here the thyroid gland is unusually active with or without a marked increase in its size. This condition is most commonly called "exophthalmic goiter," though an excessive thyroid secretion may be present without the exophthalmos, and, rarely, the exophthalmos may be present without the goiter. Parenthetically, the use of a physician's name to identify this disease is confusing. Parry discovered the syndrome first (1786). Flajani described it again later. Graves explained the syndrome intelligently

(1835), while von Basedow (1843) gave a better description and connected the disorder more definitely with its real cause.

A few words as to the principal causes of this complex disease may facilitate our study of its diagnosis. Three great factors must be taken into consideration: Focal infections; fright and emotional affections and the hereditary thyroid instability so well emphasized by Leopold Levi and discussed previously. Fright and excessive emotions are not uncommonly connected with the onset of a severe degree of exophthalmic goiter and Cannon's recent researches into the relation of the emotions to adrenal excitation may be the basis of a satisfactory explanation as to how this is caused. For instance, it is quite possible that the undue stimulation of the adrenals thus brought about may so decidedly push the thyroid pendulum as to cause it to swing very much more rapidly and widely than is normally the case, while the resulting dyshormonism may prolong the effects, for the thyroid itself is just as susceptible to the thyroid hormones in the blood as are any of the other organs of the body.

Toxemia, usually of bacterial origin, is probably the most common cause of this disease, and a careful study very often will reveal some focus of infection in one part of the body or another. Most common among these sources of bacterial poisoning are the tonsils, nasal fossae and adjoining sinuses, teeth and gums (and especially around the roots of the teeth), colon (especially the angles), gall bladder and pelvic organs; probably in the order mentioned. Undoubtedly there is also a connection between the incidence of hyperthyroidism and the gonads, especially in women, and the frequency of this disease in women, about 10 to 1, and the common relationship of menstrual disturbances with it, and vice versa, are sufficient confirmation of this. That these gonad disorders are usual in individuals with that subtle disorder named *"l'instabilite thyroidienne"* and that an hereditary defective thyroid substratum favors the onset of dysthyroidism, is well borne out by those who are in the habit of making a thorough anamnesis.

Aside from the two symptoms embodied in the name—exophthalmos and goiter—symptoms which we need not dilate upon here, the most obvious diagnostic finding is the serious change in the heart action. Tachycardia is practically the rule, the pulse ranging from 120 to 180 beats per minute. With this is an extreme degree of nervous irritability or sympatheticotonus, a good part of which, in the estimation of the writer, is due to the functional adrenal and circulatory changes, although there are cases in which these nervous manifestations have nothing to do with the heart. The cardiac excitability—it is often of a heaving, pounding nature—is responsible for the pulsation not merely of the goiter itself, but of various vessels throughout the body, and this persistent beating in the head, the abdomen and especially the

throat and neck is a very uncomfortable symptom. The undue strain on the heart often causes dilatation and even incompetency. Myocarditis is the most common and serious result. Some writers mention the auscultation of a murmur over the goiter.

As might be expected, the metabolism is decidedly plus. All the cells are working overtime as a result of the excessive thyroid stimuli and this is doubtless responsible for the hyperthermia which is quite common in the well marked cases of this disease. It also accounts for the loss of weight (despite the not infrequently increased appetite and intake of food), the increased perspiration and, probably, for the sharpened mental activities. In this connection one of the difficult features of hyperthyroidism is the control of the mental status with its disturbances of concentration in work and its effects upon insomnia. It has been remarked by several writers, and especially by Leonard Williams, of London, that among the earliest signs of excessive thyroid action is a tendency to genius, such individuals have great ideas, lean to literature or the arts, take up fads, and are far from dull in their studies or their work.

With the decided effects of myxedema upon the skin in mind, one would expect some opposite changes in the skin in this opposite condition, and this is the case. The skin is usually thin and delicate, is moist and well nourished by a very good blood supply. The skin reddens under the slightest local or emotional influence and the sweat glands become active on the least provocation until the hyperidrosis is more than a nuisance. Occasionally this is one of the earliest symptoms and night sweats of thyroid origin have led the diagnostic scent away from the right trail

The toxemia, sympathetic irritability and cardio-vascular excitability together form a combination which may produce many and varied symptoms only a few of which need be enumerated, i. e., tremor, twitchings of the eyelids and face, restlessness, insomnia and often a decided neurasthenia. Myasthenia with an aggravating fatigue and much discomfort on exertion are usual and to be expected in a disease in which the hormonic balance is so thoroughly disorganized.

The late symptoms of exophthalmic goiter include serious heart changes both in the sounds and the rhythm. Heart failure is a common cause of death from this disease. Dyspnea and severe diarrhea are also ominous signs when found accompanying other signs of hyperthyroidism.

SECTION IV. CHAPTER 4

A METHOD OF TESTING THYROID FUNCTION

Many times the reaction of an individual to organotherapy serves as a fairly good index to the condition of the endocrine glands which correspond to the gland from which the extract was made. That is to say, individuals with a sensitiveness in a given gland are likely to react more quickly to organotherapy than those in whom there is an apathy. This is more particularly true of the thyroid, and many hundreds of physicians have given thyroid extract to patients and in a short time had to discontinue it because it made them nervous and irritable, unduly stimulated the heart and evidently was not accomplishing what was desired.

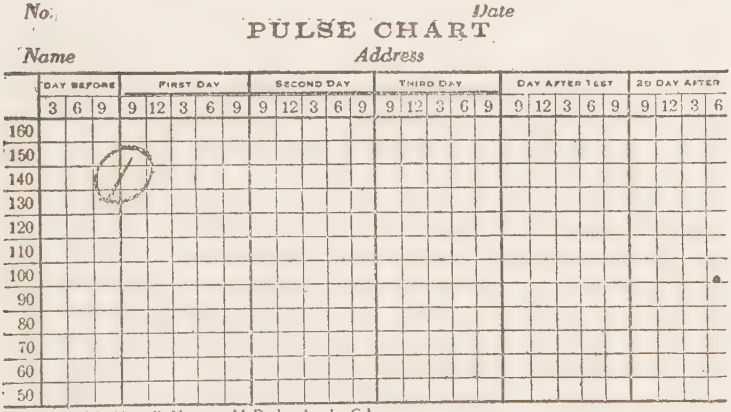
Routine Thyroid Feeding. Based upon a number of clinical experiences of this character, I have devised a very simple, but none the less useful, method of testing thyroid function, which was announced originally in the *New York Medical Record,* August 3rd, 1918. The test consists of giving definite and increasing doses of thyroid extract, with a suitable inert excipient, in a uniform and routine manner, while a careful study is made of the pulse, and any other symptoms which may occur. The information obtainable in this manner is of much service, for it amounts virtually to a differential diagnostic measure in the study of goiter.

It will be recalled that from the secretory standpoint there are two distinct varieties of goiter: (1) the simple enlargement of the gland, which appears to be an effort on the part of the organism either to supply an increased demand for its particular product which may be deficient, or to produce a greater supply than usual because of an increased demand for it; and (2) the hypertrophy which is due to some extra-glandular cause, such as toxemia or any form of irritation. The former, or simple goiters, are a useful attempt on the part of the body to render the best service possible under the circumstances and usually are benefited by a course of treatment which includes the administration of thyroid, iodine, etc., which thus tends to supply the need, in part at least, and render the friendly enlargement of the gland unnecessary. Parenthetically, in these cases of simple goiter, the administration of S. F. No. 18, *Caps. Iodized Thyroid Co.,* which contains a suitable dose of thyroid extract, iodide of iron and nuclein, serves very satisfactorily to supply the right kind of stimuli in such circumstances.

In the other class of cases, however, the conditions are decidedly different, for the thyroid gland is being overworked, and driven faster than normal. This is usually brought about (1) by the toxins absorbed from foci of infection, (2) from emotional

disturbances or (3) from deranged functions of some of the other endocrine glands. In such cases, the thyroid gland is more sensitive and hence more unruly; and just as the hypertrophy differs very materially in origin, so it differs in its responsiveness to thyroid treatment. In fact, what would be most beneficial in simple goiter would be most detrimental in the goiter due to hyperthyroidism, and the administration of my "Thyroid Function Test" enables one to differentiate the early functional stages of thyroid sensitiveness, i. e., between latent hypo- and hyperthyroidism, and thus accomplish something worth while in the treatment.

The materials for the thyroid function test consist of four doses each of a half, one and two grains of thyroid in graduated capsules together with a chart similar to the one illustrated (Fig. 1), to which is attached printed instructions as follows:


No. Date

PULSE CHART

Name Address

	DAY BEFORE			FIRST DAY					SECOND DAY					THIRD DAY					DAY AFTER TEST					2D DAY AFTER				
	3	6	9	9	12	3	6	9	9	12	3	6	9	9	12	3	6	9	9	12	3	6	9	9	12	3	6
160																											
150																											
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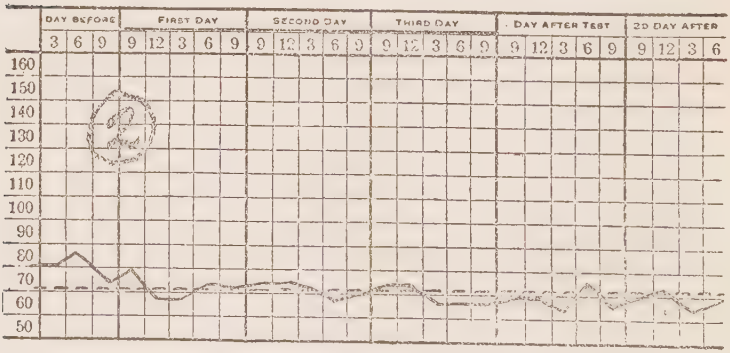
Instructions for Using the Test. Each package of "Thyroid Testing Capsules" contains 12 capsules of three graduated strengths and sizes. A pulse chart accompanies each, with explicit instructions as to how to fill out the record.

After the consultation, at which the first pulse-counting is done and recorded, the patient counts the pulse again at 6 and 9 o'clock; and the following morning commences to take the four *small* capsules at 8, 10, 12, and 2 o'clock with a swallow of water, recording the pulse five times a day—at 9, 12, 3, 6, and 9 o'clock. On the second day the four *medium*-sized capsules are taken at similar hours and the pulse is again recorded under as nearly identical conditions as possible, and at the same hours.

During the third day the four *large* capsules are taken at the same hours as previously and the pulse is again recorded as before. The fourth day, or the "first day after" finishing the ingestion of the capsules, the pulse is recorded as before and again during the forenoon of the fifth day ("second day after") when the chart is completed (and plotted, if convenient), the physician is consulted and the data thus secured carefully studied.

It is important to watch for symptoms such as irritability (temperamental or nervous), twitchings (of the eyelids, lids, fingers, etc.), breathlessness and other nervous manifestations. If it should happen that on the second or third days these symptoms are present *and prominent,* the remaining capsules should not be taken; *but the chart is completed,* while on its reverse side



a brief statement is made of the symptoms giving the time of onset and other related facts.

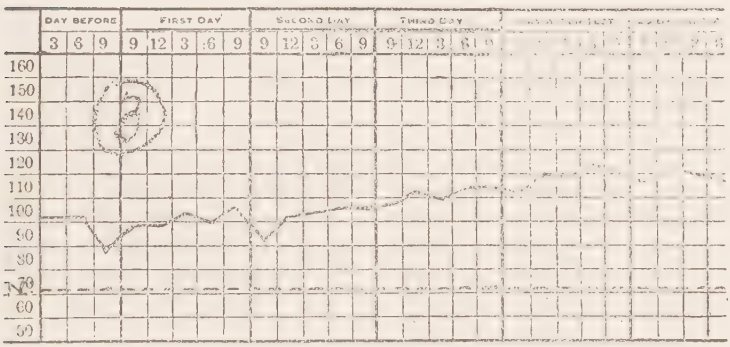
Note: Take the pulse under as nearly uniform conditions as possible, preferably before eating, after a ten minute rest and sitting. Mark the chart in the proper square with a dot at approximately its relative position, e. g., 72 would be just above the 70-line, 86 would be about the middle of the space between the 80- and 90-lines, etc. Be regular and persistent. The information thus obtained is worth all of your trouble!

The Clinical Reaction to the Test. The reaction of the patient to this routine administration of uniform doses of thyroid varies very materially, depending upon the factor that we are attempting to discover. In the apathetic hypothyroid cases, practically no difference in the pulse figure is found, and as in these cases cardiac action, like practically every function of the body, is lazy and slow, the pulse figures are low and remain so.

The reaction to the thyroid testing capsules in a case of func-

tional hypothyroidism which had not yet advanced to a stage where the usual findings of myxedema are noted is nicely illustrated on the accompanying chart (see Fig. 2). Here it will be noted that the pulse is below the normal and does not seem to be influenced whatever, even by the heavy dosage of thyroid which is given on the third day.

In the normal individual, on the other hand, the thyroid feeding is going to temporarily stimulate the thyroid function, and hence, through it, the heart rate, and it is customary, during the third day of taking the capsules, for there to be an increase in the pulse, which, however, is due to the administered thyroid extract rather than to any excess of the thyroid hormone which may be produced in the body; and since these products are destroyed

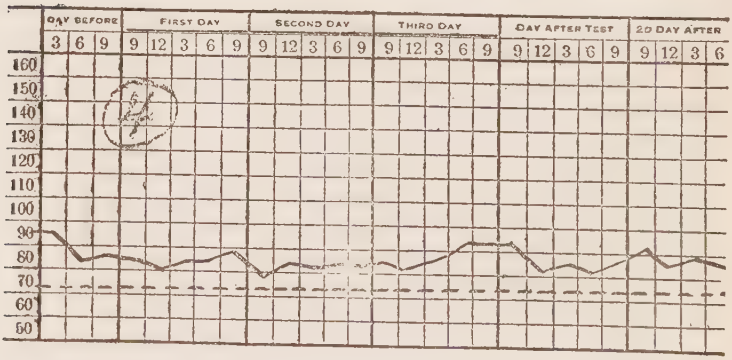


quite rapidly, the cardio-stimulant action merely lasts during the time of the greatest dosage of thyroid *and comes down to normal again the day after.*

On the other hand, in the various stages of thyroidism, the pulse findings are characteristic: the greater the susceptibility, the wider the range. First of all, as will be noted in the accompanying chart (Fig. 3), the average pulse rate is somewhat higher than normal, and there is also more irregularity than usual. Early in the administration of the thyroid, the pulse begins to be more rapid until, during the height of the temporary gland feeding, it may reach well above any possible normal figure—100, 110 or even higher. Since this stimulus is not entirely due to the product which has been administered but to the increased activity of the supersensitive gland, following the removal of the medication, i. e., "the day after" and "the second day after," *the pulse still remains up* because the thyroid is working overtime, as is

indicated very clearly on the chart. In fact, in well defined hyperthyroidism with tachycardia this test should not be used, nor need it be, for the diagnosis should be clear without it, and in latent cases in which there is an unexpected degree of thyroid sensitiveness, it will be noted that the routine advice calls for the omission of the last four capsules—the largest doses—but the continuation of the pulse tracing, with a note to that effect upon the chart. In such cases, the variations in the pulse findings will not be so exaggerated, merely because the test has not been completed, but the indications are equally obvious and helpful.

The Discovery of Latent Thyroid Conditions. This test is more useful in the discovery of thyroid apathy or a latent degree of thyroid sensitiveness than in the diagnosis of frank

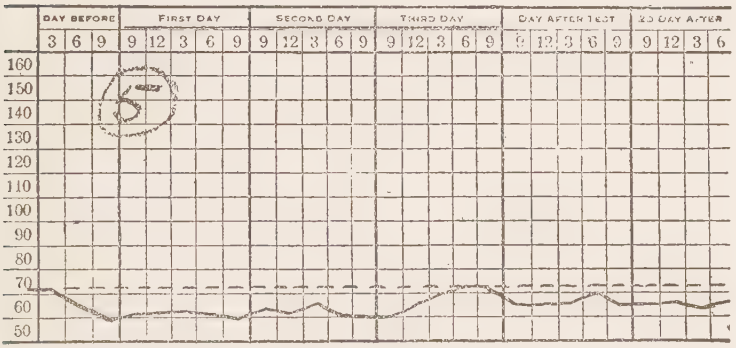


hyperthyroidism, for reasons which will be clear. Two out of many hundreds of cases that have been tested in this manner showed charts which were quite unexpected and worthy of comment. The first was an individual with a highly nervous attitude, staring eyes, fine tremor, sweating palms and general sympathetic irritation. He was sent to me as a "typical case of hyperthyroidism," yet some of the findings were missing, especially the fact that the pulse was approximately normal. A thyroid function test was made and the following chart secured (Fig. 4), and later an X-ray examination of the chest showed a sub-clavicular tumor of considerable dimensions. The sympathetic irritation was due largely to the pressure of this intrathoracic tumor, and the patient did not have "typical hyperthyroidism" after all.

Another case of an opposite character had a large goiter which was about to be operated upon for cosmetic reasons. The physician about that time happened to hear of this test, tried it and

later sent me the accompanying chart (Fig. 5), from which it seemed clear that the patient had a well defined degree of thyroid inactivity, and at my suggestion various other symptoms of Hertoghe's disease—*"myxedeme fruste"*—were discovered, the patient was given medication calculated to stimulate the thyroid and ovarian functions, and the goiter almost disappeared eventually, and the menstrual difficulties, which were quite prominent, were controlled simultaneously. In this particular case, the thyroid function test saved an operation by giving broader information in regard to the patient.

The Test in Chronic Disease. Still one other class of cases may benefit materially from the use of this test: I refer to the chronic toxic and nutritional disturbances such as rheuma-



tism, neurasthenia, tuberculosis, etc., in which elimination is very much below par and there seems to be a radical reduction in the oxidizing process. In such cases, a thyroid function test may indicate a marked degree of thyroid apathy and direct attention to the possibility of stimulating this deficiency, with decided prospects for benefit from the obviously necessary thyroid therapy. It is perfectly true that many such cases may receive benefit from the use of thyroid extract without the test, but there is a much greater satisfaction in having a definite reason for each procedure when this is possible.

My reference to tuberculosis calls for a word of explanation and caution: Many tuberculous persons have a well defined thyro-adrenal insufficiency (see Sec. V, Chap. 2), and the thyroid function test indicates this clearly, so does the blood pressure and the uranalysis. This naturally calls for obvious associated gland support that should receive attention. On the other hand, since

the thyroid gland is expected to react to stimuli of a toxic nature, a latent degree of hyperthyroidism indeed may be present and easily discoverable following this test, in which case any glandular treatment which might be in order would be the opposite from that given to the other tuberculous persons in the large class mentioned previously. In such cases instead of using the cell stimulating *Caps. Adreno-Spermin Co.*, a preparation containing pancreas, which tends to neutralize sympathetic irritability, would be better (see Sec. V, Chap. 6).

It has been said that this thyroid function test is nothing but the administration of thyroid extract and the usual noting of the patient's reaction, but unfortunately most of our experiences of this character have been our failures, and our clearest recollections about them were the remarks made about the uncomfortable feelings which resulted from the administration of the thyroid extract for a week or two, and caused us to stop it at once. Further, the fact that this test is ready to use, that there are printed instructions and a chart available, directs attention to and makes convenient a measure which ordinarily may not be thought of; hence I feel justified in emphasizing the importance of this procedure, not merely in the differentiation of goiter as indicated, but in the search for scientific reasons for the use of thyroid extract as a part of the treatment in a given case.

SECTION IV. CHAPTER 5

THE ADRENAL GLANDS IN HEALTH AND DISEASE

Perhaps more profitable research has centered around the adrenal glands during the past twenty years than around any of the other glands of internal secretion. At least many epoch making discoveries of their important role have been made quite recently.

Unfortunately the clinical application of this new knowledge has not been very extensive as yet; and many times the physician's sole appreciation of adrenal disease consists of a hazy recollection that Addison's disease is said to be a tuberculous involvement of the adrenal glands—and that it is incurable.

Some things about the adrenals are very well known. We are in the habit of using adrenalin almost every day and know that it exerts a decided influence upon the circulatory system, both in physiology and in therapeutics. We also know that the adrenin continuously produced by the adrenal medulla is the principal regulator of vascular tone and that it performs a number of other

useful services for the body. But, somehow or another, it is the exception to find a proper clinical appreciation of the importance of the work of the adrenals and how easily their functions may be influenced slightly or seriously with corresponding minor or important effects on the body as a whole.

Fifteen years ago T. R. Elliott, of London, showed us that adrenin virtually controlled the autonomic and sympathetic nervous systems. Sergent, of Paris, had already proved this relationship in numerous experiences in his clinical work. Still more recently Cannon, of Harvard, has given us an entirely new conception of the extreme importance of adrenin to the human economy especially in so far as its variations are related to the emotions.

Some Points About Adrenal Physiology. A brief exposition of the physiology of the adrenal glands will prepare us for a better understanding of their secretory disorders. The chromaffin hormone, otherwise known as adrenin, arising from the medullary portion of the adrenals, as well as in other chromophil cell collections in different parts of the body, exerts a very remarkable and extended influence upon numerous structures which are controlled by the sympathetic. Adrenin raises the blood pressure and has much to do with its maintenance at the average level; it dilates the pupils and excites the flow of tears and saliva; it contracts the minute muscles of the hairs (erectores pilorum); undoubtedly it is concerned with the function of the sweat glands and, in fact, the blood supply of the skin and, in addition to all this, it seems to have a certain influence upon the gastric, uterine and intraabdominal muscles in general.

Adrenin is probably the principal factor in the maintenance of the normal tone of the body, and disturbances in its production disorganize the so-called "sympathetico-tonus," causing it to be deficient or abnormally increased as the case may be. The condition known as "adrenin sensibility" is now being used as the basis for several tests for sympathetic functioning which will be referred to later.

The adrenals are particularly susceptible to what have been termed the "emergency conditions." Cannon's well checked experiments have definitely proved that the emotions, including pain, rage, fear and hunger (perhaps it will be shown later that even worry has a similar effect) influence the secretory powers of the adrenals, with an immediate response due to the hyperadrenia thus produced. This condition passes rapidly because adrenin is oxidized with unusual facility, and as soon as the glands have been sufficiently overworked and the stimulation continues with no opportunity for recuperation, a serious condition of hypoadrenia supervenes.

While comparatively very little therapeutic advantage has been taken of the results of this work, we can now see rational expla-

nations for a number of phenomena which quickly can be called to mind. Practically the whole of the results of Crile's investigation of "the kinetic system" and his now fairly well known method of "anoci-association" are really dependent upon the prevention by suitable measures of any undue stimulation of the adrenal glands, and hence the serious consequences of acute hypoadrenia are thereby forestalled. It will be recalled that Crile emphasized the fact that the kinetic system embraces the adrenals, thyroid, brain and muscles, which co-operate to "drive" the body. The adrenals are probably the most important of these kinetic organs and the method of pan-anesthesia named "anoci-association" consists in supplementing the usual anesthetic measures by removing such mental and nervous stimuli (by preventing fear and pain and by "blocking" certain nerves) as would tend to stimulate the adrenals and by their depletion bring on shock and collapse.

Before considering the symptomatology of the functional adrenal secretory dyscrasias, it should be recalled that not only are the emotional factors already referred to capable of causing this adrenal syndrome, but that certain of the hormones produced in other organs, when present in the blood stream in unusual amounts (see further references to this in the chapter on the ovaries) may have a similar stimulating effect. We must also remember that toxemia of intestinal or bacterial origin exerts a like influence and that it has been shown that conditions associated with extremely high blood pressure cause adrenal disorder, probably by producing intra-adrenal hemorrhages. One of the best established "symptoms" of senility is of adrenal origin.

With these facts in mind we can understand that severe emotional conditions, sudden or prolonged; acute infectious diseases with the invariable accompanying toxemia; and chronic infections, as tuberculosis or intestinal stasis (which is, after all, practically a chronic infection with mechanical involvement added) would be likely to bring about certain changes in the activities of the organism as a result of the influences due to adrenal derangement.

Hyperadrenia. Hyperadrenia is not nearly so common a symptom as hypoadrenia, although it needs must be just as frequent, for the adrenal depletion of which we shall shortly speak is really a terminal condition which results from the exhaustion following excessive stimulation. The reason that hyperadrenia is not more commonly detected is probably due to the fact that adrenin is oxidized in the blood with great rapidity, and that if large quantities of it happen to be brought forth, they are destroyed very shortly after they are produced. Confirmation of this destructive influence is noted following the use of adrenalin for therapeutic purposes, as well as in many experiments on animals which uniformly show that once this hormone

gets into the blood, it is very quickly destroyed. Incidentally this is also emphasized by the fact that adrenalin is not as effective or suitable for prolonged adrenal support as adrenal substance for while adrenalin undoubtedly homostimulates the adrenals it does so suddenly and actively, but the effects are ephemeral while on the other hand the use of the total gland favors a re-establishment of the depleted adrenal functions, though the action is slower.

It will be proper to enumerate several clinical findings which are probably of adrenal origin, since the treatment is largely preventive rather than direct, for to realize that certain factors are unduly stimulating the adrenals is to realize that these factors must be abated.

An unusual tendency to goose pimples, without any ordinary reason therefor may be directly due to this condition. Probably this accounts for the not uncommon association of this phenomenon with fright. Chills, which are merely severe vaso-motor disturbances with muscular spasm, are commonly produced artificially by injections of adrenalin (especially following its use in the control of asthma), and I am by no means sure that this chief manifestation of malaria is not due to a temporary and excessive stimulation of the adrenal glands by the sudden unloosing of the toxins of the plasmodia. Further, the severe reaction following this positive phase of malaria, with its prostration, asthenia and depression, stimulates the symptom complex of hypoadrenia, as we shall shortly see.

In studying the relation of the adrenal glands to the toxemia of tuberculosis, Pottenger remarks that the continued stimulation of the adrenals and the continued pouring into the blood stream minutely increased amounts of adrenin, has the effect of producing a prolongation of the condition which is originally brought about by sympathetic stimulation. It is suggested that this condition of hyperadrenia is responsible for the dry mouth frequently seen in tuberculosis, and that other symptoms of sympathetic origin such as the sudden and seriously impaired digestion and, particularly, the rapid heart action, are really the results of excessive adrenal stimulation. Without a doubt hyperadrenia unduly stimulates the thyroid and vice versa, hence the symptomatology of adrenal excess and hyperthyroidism is similar, and it is difficult to differentiate the origin of a given disorder.

It is quite possible that certain cases of purely functional hypertension, with no renal, cerebral or vascular findings demonstrable, are really due to hyperadrenia, usually of toxic origin. At least the interesting though academic researches of Zimmern and Cottenot, of Paris, seem to confirm this. They were able to reduce very high tensions by properly dosed roentgenization of the areas over the adrenals—to my mind a very serious undertaking. Parenthetically some quite profitable studies of the treat-

ment of functional hypertension have been based upon this fact and on the well known antagonism exerted by the pancreas upon adrenal function. This is considered more in detail in Section V, Chapter 10.

There is still another form of hyperadrenia which must be mentioned though it is very rare. I refer to the condition known as "hypernephroma," which is an excessive proliferation of the adrenals usually involving the corticular tissue more than the medulla. The chief manifestation of this is a remarkable increase in the development and growth in early life (this is much more common in young subjects) with premature sexual development. Bullock, Sequeira and others have demonstrated a relation between the presumed internal secretion of the adrenal cortex and the gonads. At all events in cases of this disease the findings are chiefly referable to the gonad functions—a child of eight or nine may be quite as large as an adult with marked overdevelopment, physical and functional, of the genitalia, and hypertrichosis. It is a difficult, practically hopeless, surgical condition.

Adrenal Insufficiency. Since the adrenals are so extremely susceptible to so many outside influences it is likely that they would be easily "worn out" and, as a matter of fact, functional hypoadrenia is as common a condition as any endocrine manifestation. From a practical standpoint, this is an extremely important symptom complex.

It is quite some years since Sajous began to emphasize the importance of this condition, and while his opinions were scouted and some of his ideas declared visionary it must be admitted that our present knowledge of this subject is very much in harmony with the following quotation from Sajous' monumental work: "Functional hypoadrenia is the symptom complex of deficient activity of the adrenals due to inadequate development, exhaustion by fatigue, senile degeneration, or any other factor which, without provoking organic lesions in the organs of their nerve paths, is capable of reducing their secretory activity. Asthenia, sensitiveness to cold and cold extremities, hypotension, weak cardiac action and pulse, anorexia, anemia, slow metabolism, constipation and psychasthenia are the main symptoms of this condition."

Hypoadrenia is a complication of all the serious acute infectious fevers, since the adrenals are so intimately connected with the "driving" of the body and are so susceptible to toxemia, that the ultimate reduction of the accustomed adrenal stimuli is responsible for a slowing down of many of the sympathetic-controlled functions of the organism. Too often this sympathetic asthenia is the actual cause of death from disease of this character.

There are three forms of hypoadrenia which differ sufficiently from one another to be discussed separately:

(1) *Functional Hypoadrenia*—a temporary deficiency in the production of the chromaffin hormone shown most frequently by a tardy response of the circulatory system to its accustomed stimuli and the development of a condition of circulatory inefficiency, the so-called "hyposphyxia" of Martinet. This is a condition of circulatory semi-asphyxia with venous stasis, insufficient arteriolar circulation with cold extremities and occasional slight blueness (often a mottled appearance) of the skin on different parts of the body, especially the exposed parts. In such individuals the blood pressure is usually very low, 90-100 mm., although it has been shown that extreme degrees of tension may cause a functional insufficiency of the adrenals by localized hemorrhage into the glands.

Urticaria and other severe vasomotor skin symptoms are among the well marked findings in persistent hyposphyxia, while lesser degrees may cause flushings and sensations of passing distress localized in various areas of the skin. The adrenal origin of some forms of urticaria is seemingly confirmed by the occasional "miraculous" disappearance of large and most uncomfortable wheals following a single hypodermic injection of from 5 to 10 minims of adrenalin solution.

Besides the circulatory syndrome the muscular and nervous manifestations are important. Asthenia is the rule and muscular tone (both striped and unstriped muscle) is poor. Exertion is impossible and "the fatigue syndrome" is prominent. The intestinal musculature is inactive and stasis, a common cause of hypoadrenia, is also a common result of it. According to Tom Williams, mental exertion, even the simplest, often causes so much weariness and exhaustion as to be prohibitive. Mental elasticity is lost and there is both mental and physical depression with the fear that the individual cannot now accomplish their accustomed good mental work; and the story that they "have lost their nerve." With this one frequently notes a fearfulness of making wrong decisions and a vascillating and indecisive frame of mind. This is the most usual form of adrenal insufficiency. It is chronic both in origin and in its course. The greatest single cause is chronic toxemia either of alimentary or focal infective origin. Fortunately the control of the cause and suitable "adrenal support" (see Sec. V, Ch. 1) is followed by very encouraging results.

(2) *Progressive Hypoadrenia.*—Here we expect more than the mere functional derangement just discussed. This is really another name for the disease we have been taught was first named by Addison in 1855 which, like all organic diseases, may be seen in differing forms and stages. The main symptom is the aggravated asthenia with marked myasthenia. In well advanced cases there is a localized bronzing of the skin and mucous membranes due to the deposition of a dark pigment of undecided origin. Extreme cardio-vascular debility is the rule and the blood

pressure may be as low as 30 to 50 mm. Hg. Varying gastro-intestinal disturbances are usual. Fortunately this disease is rare and unfortunately its outcome is hopeless, though temporary relief has followed adrenal medication.

Lawrence connects hypofunction of the adrenal glands with weakness and apathy, marked fatigability and a tendency toward vertigo. These are merely variations in degree of the classical symptoms first reported by Addison.

(3) *Terminal Hypoadrenia.*—This is the extreme functional adrenal insufficiency which has already been briefly mentioned. This occurs in the final stages of fatal infectious diseases. For instance the principal clinical manifestations of Asiatic cholera (the algid stage) are adrenal in origin and, remarkably enough, have been promptly and successfully controlled by heroic doses of adrenalin, for in such cases the tolerance to the drug is apparently greatly increased and as much as an ounce of the commercial 1:1000 solution well diluted with saline solution has been given intravenously during a single day with splendid results (Naame).

Shock, collapse, cardiac failure and distressing asthenia are terminal findings in this class of cases. Distressing meteorism is present and is presumably due to functional intestinal paresis which, by the way, can be experimentally produced by fright or toxemia and the resulting acute hypoadrenia. With these dread symptoms there is often found a noticeable reduction in the reaction of the organism to urgently needed medication, for with the adrenal activities suspended, the responsiveness of the body to stimuli of this character is practically nil.

The ominous sign of a suddenly reduced temperature is often seen and is due to the same cause. In such cases one can invariably produce Sergent's "*ligne blanche surrenale*," a dermographic sign which consists of a white line upon the skin which follows penciling the abdomen with the finger nail, and sometimes lasts for two or three minutes. This valuable clinical sign is said to be pathognomonic of acute hypoadrenia and is very easily elicited.

In cases of the character just considered, despite the severity, the therapeutic test is often both encouraging and confirmatory, for the response to hypodermic or intravenous injections of adrenalin solution and, in many cases, the early administration of this remedy by mouth, is many times nothing short of marvelous. At times I feel that this phase of adrenal medication deserves to be classed with thyroid in myxedema and quinine in malaria. At least it is worth recommending both as a prophylactic of such ultimate results, and as a last resort in their treatment.

Neurasthenia as an Adrenal Syndrome. The minor form of functional hypoadrenia is more common than some have appreciated, and the fact that there is a psychic origin as well as the other physiologic causes already considered, allies it to the fash-

ionable neurasthenia of today. In fact some have stated that what is improperly called "neurasthenia" is not a disease *per se*, but really a symptom complex of ductless glandular origin and that the adrenals are probably the most important factors in its causation. Campbell Smith, Osborne, Williams and others, including the writer, have directed attention to the importance of the adrenal origin of neurasthenia (though a pluriglandular dyscrasia is practically always discoverable) but so far this is not understood as well as its frequency and clinical importance seem to warrant.

The subject is too large to receive exhaustive consideration here, and already I have published a small book entitled "The Adrenal Glands in Every-day Medicine," a copy of which will be sent to interested readers, on request. However, a few quotations from the literature will firmly establish the importance of this angle from which to study this common and annoying symptom complex.

Quoting first from the *Journal A. M. A.* (Dec. 18, 1915): "The typical neurotic generally has, if not always, disturbance of the thyroid gland. The typical neurasthenic probably generally has disturbance of the suprarenal glands on the side of insufficiency. The blood pressure in these neurasthenic patients is almost always low for the individuals, and their circulation is poor. A vasomotor paralysis, often present, allows chillings, flushings, cold or burning hands and feet, drowsiness when the patient is up, wakefulness on lying down and hence insomnia. There may be more or less tingling or numbness of the extremities."

Again Kinnier Wilson in his monograph on "The Clinical Importance of the Sympathetic Nervous System" makes the following pertinent remarks: "Many of the common symptoms of neurasthenia and hysteria are patently of sympathetic origin. Who of us has not seen the typical irregular blotches appear on the skin of the neck and face as the neurasthenic subject 'works himself up into a state'? The clammy hand, flushed or pallid features, dilated pupils, the innumerable paresthesias, the unwonted sensations in head or body, are surely of sympathetic parentage. In not a few cases of neurasthenia symptoms of this class are the chief or only manifestations of the disease. Here, then, is a condition of defective sympatheticotonus; may it not have much to do with impairment of function of the chromophil system? . . . There does not appear to me any tenable distinction between the asthenia of Addison's disease and the asthenia of neurasthenia. Cases of the former are not infrequently diagnosed as ordinary neurasthenia at first. It is difficult to avoid the conclusion that defect of glandular function is responsible for much of the clinical picture of neurasthenia."

Later this same author makes the following apothegm: "Sympathetic tone is dependent on adrenal support, and until the

glandular equilibrium is once more attained sympathetic symptoms are likely to occur."

Adrenin Sensibility. As the art of clinical diagnosis is perfected we are having brought to our attention numerous "tests" of function and several of these are dependent upon a condition of hormone balance involving the adrenals. This has been called "adrenin sensibility" and the best known test based on this is that of Loewi which consists of instilling a few drops of adrenalin solution (1:1000) into the conjunctival sac. Without going into a rather complicated subject—the study of the hormone balance is not yet very simple—marked dilatation of the pupil occurs in 30 to 60 minutes in pancreatic diabetes, and this test has been used to confirm suspicions as to the waning internal secretory powers of the pancreas of which more will be said in a later chapter.

This same test is of value in Graves's disease and a dilatation following conjunctival instillations of adrenalin solution has also been proposed as a means of determining thyroid hyperfunction. Space cannot be taken to explain the *raison d'etre* of these tests and I recommend them as confirmatory measures only.

Schultz has advanced an almost identical test for incipient dementia praecox and asserts that marked mydriasis will follow in about ten minutes after the instillation as above and that the pupillary dilatation will last as long as half an hour. Parenthetically it may be well to remark that Dunlop Robertson believes that the catatonic type of dementia praecox is due to hyperadrenia.

SECTION IV. CHAPTER 6

THE DISORDERS OF THE PITUITARY BODY

The study of the various phases of endocrinology seems to have advanced in waves; and our knowledge of the clinical and physiological relations of the hypophysis or pituitary body is a good example of this. Thirty years ago quite an interest was aroused in this remarkable gland by the publication of Marie's classical study of the pathology of acromegaly and his correlation with it of disease of the pituitary gland. Nearly ten years later—in 1894—a greater wave of enthusiasm and interest was launched by Sir Edward A. Schaefer who made the discovery that the pituitary was a gland of internal secretion. Numerous investigations were initiated by this report, many of which have added materially to our knowledge of this subject.

The third and greatest wave of all must be connected with the

name of Harvey Cushing, and this has brought us to the present high tide of knowledge of the subject, for, thanks to the results of the years which Cushing has spent in investigating pituitary disorders, the profession is better able to realize the comparative frequency of affections of this gland.

Cushing's monograph, "The Pituitary Body and Its Disorders," has been called the most complete and useful monograph in English; and the numerous publications of reports of his work and that of his associates include the major part of our present knowledge on this subject.

Physiological Considerations. An appreciation of the essentials of the physiology of this gland, its interrelation with the other endocrine organs, and its influence upon the activities of the body, will enable us to detect the several results of functional pituitary dyscrasia during their early stages, before such obvious and serious changes as those present in acromegaly have established themselves.

It must be recalled that structurally the pituitary gland is divided into three parts: the largest anterior lobe being a typical glandular structure; the much smaller posterior lobe having the histological appearance of nervous tissue, while the very small connecting portion, usually called by its Latin name *"pars intermedia,"* is made up of a mixture of both kinds of these cells. Each of these portions produces one or more chemical substances or hormones, the functions of which are not all fully understood. Without going into detail, it may be stated that the anterior lobe produces a hormone which regulates the growth of the body. This was isolated recently by T. Brailsford Robertson at the University of California, and has been called by him "tethelin." In both physiology and organotherapy this substance promotes growth, especially that of bone and connective tissue; and it is anticipated that many useful advances in organotherapy will follow the clinical-experimental study of preparations derived from the anterior lobe of the pituitary.

From the posterior lobe there is secreted, presumably directly into the cerebro-spinal canal, a series of hormones which play an important part in the control of metabolism, especially that of the carbohydrates. They also influence in some subtle way the sympathetic nervous system quite similarly to the chromaffin hormone from the adrenals. Much clinical use has been made of the extract of the posterior lobe, and undoubtedly it exerts a very wonderful pharmacological influence upon unstriped muscle and particularly upon the uterus in labor. A diuretic hormone of considerable activity is also produced in this gland, some saying that it arises in the pars intermedia and others in the posterior lobe.

The pituitary body as a whole is very intimately connected with sex development as we shall shortly see: and is able to

assist the thyroid and gonads vicariously when this becomes necessary. These complex relationships complicate the study of the subject, and it might just as well be stated right here that it is not a simple task accurately to differentiate between the results of deficiencies of these endocrine glands, for their relations are so intimate that it is quite impossible for one to be affected without some chemical reflex influence being brought about in the work of most or all of the others; and as these glands seem to exert a compensatory influence upon the work of those glands with which they are correlated, it is often difficult to determine the original gland at fault in a given case, and unless this is done, suitable treatment, organotherapeutic or otherwise, may be impossible.

We have just noted that there is a great functional difference between the parts of the pituitary. Like several other endocrine organs it is a dual one, with differing structure and physiological powers; and it is possible that clinical manifestations due to affections of one lobe may differ very materially from those due to disturbances of the other. An attempt to facilitate a differentiation between the disorders of the two lobes will follow the consideration of disease of the whole gland.

Dyspituitarism. When disorders of the pituitary gland are the result of tumors, cysts or intracellular disturbance, there may be varying secretory changes. On the one hand pressure due to the growth may prevent the normal secretory activity, while, on the other hand, the enlargement may be a pure hyperplasia with markedly increased function until the limitations of the sella turcica—the bony cup above the sphenoid bone in which the pituitary rests—cause a secondary hypofunction. Such cases are termed dyspituitarism, since varying results are produced. In fact many individuals suffering from pituitary excess have at the same time well defined evidences of pituitary insufficiency, secondary to the original trouble.

Dyspituitarism, then, is pituitary secretory dyscrasia and may include the pure hypo- and hyper-function and all grades between them and combinations of them. By careful study it is often possible to decide which disturbance is predominant and also which is the original disorder. A diagnosis of "dyspituitarism" is good; but to qualify this and go further into the genesis of the disorder, is much better.

Pituitary Insufficiency. With the fundamentals previously outlined in mind, we can expect marked changes in the metabolism as a result of insufficient activity of the pituitary gland. The most common result of insufficient function—hypopituitarism—is an undue increase in the deposit of fat which later may become a serious obesity, a condition which is probably due to the marked increase in the tolerance for carbohydrates usually found in hypopituitarism, and the abnormal desire for food and

especially for sweets with which this is quite often associated. It is not uncommon to find patients in this class eating ravenously with appetites far beyond the usual.

The cellular activities are generally reduced and the temperature is subnormal, movements slow and somnolence is a prominent symprom. Parenthetically, Cushing and his associates have remarked that hibernation in certain animals seems to be a physiological hypopituitarism. Lassitude, torpidity and drowsiness is often the first appreciated symptom. (Some years ago I saw a case with Dr. W. W. Roblee at Riverside, who would fall asleep during meals or in the middle of a sentence; and who, by the way, improved very much under pituitary medication.) Sleep is not always refreshing and tiredness is a usual complaint.

This reduced oxidation is probably due in part to an associated thyroid insufficiency. The urinary solids are reduced, but the amount of urine is often increased; and it is now believed that the majority of those suffering from extreme polyuria, or diabetes insipidus, really have a form of pituitary disease. According to Motzfeldt and others the lesion is in the posterior lobe, and the functional changes are on the side of hyposecretion.

There are well defined and almost pathognomonic retrogressive changes in the sex organs and functions. The syndrome described by Froehlich and Bartels—the so-called *"dystrophia adiposo-genitalis"*—is due to hypopituitarism, the adiposity being marked and the sex-changes characteristic.

The age at which these conditions assert themselves naturally causes variations in the manifestations. When pituitary insufficiency is present in childhood or early youth, the developmental changes are more marked. The stature is small and skeletal growth is stunted. Genu valgum is quite common. The fingers are frequently tapered and considerably shortened, with a stubby appearance. Acromicria, i. e., unusually small hands and feet, has been noted by Timme, though this is rare compared with the corresponding opposite (acromegaly) in the opopsite condition. The epiphyses may remain ununited and it is well in cases of reduced stature to have roentgen pictures made of a hand, so that if defective epiphysial growth is still present, there is hope for comparatively successful results from suitable organotherapy. On the other hand, in dwarfs showing fully united epiphyses there is little hope that the most effective therapeutic measures will increase the stature.

Temperamentally children with hypopituitarism are dull, apathetic, backward in their studies and easily discouraged. They often have difficulties with their playmates and lack both self-reliance and self-control.

The abnormalities of sex development are among the most typical results of pituitary insufficiency. The external genitals are small, the pubertial growth of hair is sparse or absent.

There may be either cryptorchism or infantile uterus with impotence or amenorrhea. The menses appear late or not at all, and if the amenorrhea is not complete, the flow is scanty and irregular. The breasts often become extremely large due both to the adiposity usually present and to the reduced gonad activity. A peculiar and quite constant finding is a tendency to development which simulates that of the opposite sex, especially in the male, in whom the public hair line is straight and the contour of the hips and chest quite female in type.

The head is often small and the face unintelligent, and the distance between the eyes narrowed. The teeth are usually malformed and broad. The skin is dry and soft, and, compared with the dry, rough skin of hypothyroidism, is quite smooth to the touch, and wrinkling of the skin, especially on the backs of the hands, with deep cutaneous furrows surrounding each digit, is mentioned as a characteristic feature by Boston. Perspiration is much reduced, even in hot weather and during exertion.

When hypopituitarism is acquired after maturity it is often the result of syphilis, and the developmental changes just enumerated are not present. Here, however, there is anaphrodisia and sexual atrophy, obesity which may be extreme with difficulty in locomotion and work, with a natural tendency to laziness and lethargy which further increases the asthenia and deposition of fat. Occasionally the fatty deposits are painful on pressure and are very similar to Dercum's disease or *adiposis dolorosa,* a condition which is probably of both pituitary and thyroid origin. This adiposity causes difficulties with the heart and breathing and edema may supervene due to fatty pericardial involvement.

Asthenia is the rule, irrespective of the extent of the obesity, and the unstriped muscles seem to be affected equally with the voluntary muscles, hence constipation is common and the bladder walls may be unduly weak with incontinence. The heart action is weak and the pulse slow and of reduced volume. The blood pressure is low, ranging from 100 mm. Hg. to as low as 50 mm. or less. The circulation is poor, the extremities are cold and sometimes edematous late in the day, and occasionally the skin exhibits the mottled appearance referred to in the previous chapter.

Several authorities have noticed epilepsy as an accompaniment of hypopituitarism. Just what is the relationship we have yet to learn, but several writers, including Cushing, have remarked that pituitary feeding caused a decided benefit to the epileptic manifestations as well as those which are more generally recognized as of pituitary origin. The therapeutic side of "endocrine epilepsy" is an important and seemingly hopeful subject and is considered further in Chapter 8 of the following section.

Hyperpituitarism. The start toward our present knowledge of the conditions associated with pituitary excess (hypertrophy and secretory activity) was made in the report of several

cases in 1886 by Pierre Marie. He called the syndrome "acromegalia" because of the usually large hands and feet which were a prominent part of the clinical syndrome. A comparison of the manifestations of increased pituitary secretion would be expected to show diametrically opposite findings to many of the hypopituitaric conditions above. For example, children with hyperpituitarism are large for their age, tall and bony framed. Their eyes are wide apart, the face is broad, the cheeks prominent and the jaw square and large. The condition of the facial bones is generally called prognathism. The teeth many times are large, broad and irregularly spaced.

Such individuals have large hands and feet, with long fingers and toes and an unusually early epiphyseal union. The hair is usually profuse, exhibits a tendency to grow low on the forehead, well up on the abdomen and, occasionally, hypertrichosis is present. The axillary and pubic hair comes unusually early and is always excessive. The skin is thick, harsh and sometimes puffy. The sweat glands are usually active.

The sexual development is excessive and in early cases precocity is to be expected and sexual irritability may be marked. The sympathetic system is well developed and highly sensitive. Hyperpituitaric individuals are often bright and keen and very excitable, though they lack the power of concentration and are indecisive. Temperamentally they are often irritable, distrustful, petulant and "difficult." They do not sleep well and insomnia is progressive as the glandular hypertrophy causes the local symptoms which will be referred to shortly.

The metabolism is plus and much accumulation of fat is rare. There may be a slight increase in the temperature, and the urinary solids are often increased. The tolerance to carbohydrates is reduced and the "carbohydrate tolerance test" is positive with 25 or 50 grams of sugar and not infrequently glycosuria is one of the symptoms of hyperpituitarism.

A urinary test for dyspituitarism is thus made possible. The high tolerance for sugar is usual in hypopituitarism. This may be easily demonstrated by giving, measured, increasing amounts of sugar or, preferably, levulose, and noting how much may be taken without glycosuria. Often as much as 250 grams can be eaten (Cushing reports a case in which 450 grams was taken) without a trace of glucose in the urine passed during the next few hours thereafter. On the other hand in the opposite secretory condition—hyperpituitiarism—there is a very low sugar tolerance, and not infrequently there may be glycosuria.

The pulse rate is occasionally increased, though not very rapid; but the blood pressure may be high, ranging from 150 to 180 mm. or more.

Both gigantism and acromegaly are the result of hyperpituitarism; but in the former instance the dystrophy has commenced

before ossification of the bones has taken place with a resultant increase in length principally. In acromegaly, i. e., hyperpituitarism after full development, the bone changes tend to thickness, hence the prognathism, protruding forehead and "heavy" facies, and the kyphotic spine not uncommonly seen.

Neighborhood Symptoms. When the secretory disturbances of the pituitary are coupled with hypertrophic changes, a series of localized symptoms are caused which are of a wholly distinct character from those due to chemical changes—the pressure or neighborhood symptoms. These are ultimate results and are practically always accompanied by changes in the size and conformation of the sella turcica which can be seen and even measured by roentgenography.

Unfortunately these pressure symptoms are often the first indication that we have dyspituitarism to contend with, and they are practically only seen in advanced cases. Under such circumstances we can expect to find supplementary evidence of the cause of the trouble by looking for the systemic chemical changes of pituitary origin which have already been enumerated. These localized symptoms are often so serious as to call for cerebral decompression and curative treatment is practically hopeless; while the general metabolic disturbances previously mentioned often may be favorably affected by persistent organotherapy.

To quote a statement from Cushing: "It is particularly important that we should learn to recognize these clinical expressions of hypophyseal disorder in the absence of brain tumor symptoms or radioscopic enlargement of the pituitary fossa, in the same way that it is important for us to recognize thyroid disorders unaccompanied by gross evidence of change in the configuration of the gland."

Neighborhood symptoms may be roughly divided into two classes: Immediate (local) and intracranial (general) pressure effects. In the former we look for the results of pressure on the structures in contact with the mass, while in the latter, those found in any brain tumor—due to the increased intracranial pressure.

Among the former symptoms are well marked eye symptoms such as bitemporal hemianopsia (blindness of the outer temporal fields of vision) due to pressure on the optic chiasma. This usually first affects color only and later form. In more advanced cases, when the tumor extends beyond the sellar edges, squint results, due either to pressure on the sixth cranial nerve (internal strabismus) or the third cranial nerve (external strabismus). As a result of still more extensive involvement, there may be pressure on the crura cerebri and disturbances of gait with a positive Babinski sign. Certain epileptoid attacks, the so-called "uncinate fits" are occasionally seen and are probably due to pressure upon the uncinate gyrus. The relationship of epilepsy and

pituitary disease is interesting and bids fair to offer a part of the solution of this problem.

Before the last of these pressure symptoms have been caused, general intracranial symptoms will have supervened. These consist chiefly of a severe intractable headache, paroxysmal in character and often affecting both temples, with vertigo, vomiting (often of the projectile type) and failing vision with later choked disc (papilloedema) and progressive destruction of the visual fields and ultimate optic atrophy.

Differentiating the Lobes Involved. It is rare that we find dyspituitarism of a single lobe, though it is possible. It is not unusual, however, to find predominating symptoms indicating that the principal trouble is in one of the lobes. If we bear in mind the varying physiological activities of the different portions of the hypophysis we will expect to find anterior lobe disorders more frequently accompanied by changes in growth and skeletal development. We have seen that with hypersecretion early the result is giantism, whereas later in life acromegaly is the result. On the other hand, hyposecretion retards growth and if it comes early the result is infantilism, while later it brings about retrogressive changes in the sex organs and manifestations.

Dystrophies of posterior lobe origin are quite different, since they account for metabolic changes which cause the adiposity and increased carbohydrate tolerance found in hypopituitarism, while the excessive secretory activity of the posterior lobe produces a relative carbohydrate intolerance with glycosuria and increased metabolism and loss of weight.

Commonly both lobes are affected simultaneously, though the effects of one lobe may be more prominent and may change at different stages of the disease. Froehlich's syndrome, for instance, is evidently due to a secretory deficiency of the whole gland.

The Cause of Pituitary Affections. Etiology is often of great service in making a therapeutically useful diagnosis. In the estimation of the writer syphilis is the chief cause of dyspituitarism, and while heredity is an evident factor, syphilis in parents and grandparents may have left an intangible susceptibility. The Wassermann test is very useful here.

New growths of the hypophysis, other than gummata, are common etiological factors the causes of which are still altogether unknown. Early organic changes in the bony pituitary fossa may restrict the proper development of the growing gland. Brain tumors, either adjacent to the pituitary or remote from it, may cause dyspituitarism by increasing the intracranial pressure and the pituitary symptoms may entirely disappear following decompression.

It has also been suggested that as the posterior lobe is supposed

to secrete into the cerebro-spinal canal, changes in the intra-spinal pressure may cause pituitary disorder.

SECTION IV. CHAPTER 7

ENDOCRINE DYSFUNCTION OF THE MALE GONADS

"Removal of the sexual glands produces profound changes in the organism, evidenced as alterations of bodily physique and of temperament. If the extirpation is made at an early period in life, the so-called secondary sexual characters may fail to exhibit themselves in the usual manner, and thus occasion the retention of infantile characteristics in place of typical features of adult form and behavior. There is reason to believe that we may properly speak of 'genital hormones' at the present time, in explanation of the undoubted chemical correlation exerted by the genital glands on other parts of the reproductive apparatus as well as on the organism in general. At any rate, the secondary sexual characters must be associated with the influence of chemical substances produced by the ovary and testis, respectively. Castration after puberty cannot modify profoundly the development of structures like the skeleton, which are already completed; but it may unquestionably bring about obvious structural and even functional changes which can be determined by careful observation."

The foregoing paragraph, quoted from an editorial in the *Journal of the American Medical Association* (May 13, 1916), is a fit introduction to my brief consideration of this subject. The "genital hormones" from the testes, like hormones from other glands, may be produced in insufficient quantities (hypogonadism) or may be absent (agonadism). Varied functional as well as structural changes result. They are not very difficult to diagnose; but the establishment of the cause is another matter.

Perhaps the endocrine dysfunction of the testes does not require a comprehensive study, for we are better acquainted with the results of increased or decreased physiological activity of these glands. An early hypogonadism virtually means essential infantilism, sexual insufficiency and maldevelopment as cryptorchidism and total absence of the testicles.

Essential Infantilism. There are several clinical forms of organic gonad disorder: Infantilism is the condition in which the glands are poorly developed or absent. Here the results are much the same as in hypoovarism, the form and function is changed, the bodily growth is altered and the secondary

sexual characteristics which normally should show themselves at puberty do not materialize.

The testicles are very small, the scrotum atrophied and the penis short and incapable of erection. Infantilism may vary in degree, and developmental changes are not always necessarily accompanied by absolute inactivity of the interstitial cells of Leydig. In this case, there eventually may be possibilities of sexual desire and azoospermia may be absent. The cause may be inherent in the sex glands themselves, but usually is due to other endocrine difficulties which are discussed elsewhere.

Cryptorchidism. The developmental anomaly known as cryptorchidism, also known as "undescended testicle," is not rare; but cases with permanent cryptorchidism are very uncommon. There may be two forms, the abdominal and the inguinal. Occasionally this condition is accompanied by testicular maldevelopment with lack of all the functions dependent upon proper activity of the Leydig cells. Again, despite complete burial of the testes, they may be functionally active, in which case there is sterility in individuals none the less potent, the sterility being purely mechanical rather than functional. Such cases obviously are not subject to the same degree of asexualism as in pure infantilism or in castrates.

I have seen many endocrine dystrophies of the gonads which were not essential, i. e., they were related to pituitary or thyroid disturbances (insufficiency) and the matter is mentioned in the chapters devoted to these subjects respectively. I recall a case of a defective boy of ten with cryptorchidism to whom I recommended my No. 2, *Caps. Antero-Pituitary Co.* I explained to the mother that I did not believe that there were no testes at all but that they had not descended. I also said that they would not likely develop at puberty if they were permitted to remain in the canal and that surgical treatment should be given before then. I hinted ever so carefully that the medical treatment (organotherapy) might help; and to the surprise and delight of all, the testes both came down after nine weeks of this treatment with nothing added but some simple dietetic admonitions. The only sad thing about the case was the comment of a colleague that it was "probably a coincidence!"

Eunuchoidism. The condition known as eunuchoidism is presumed to be an acquired disorder of the interstitial cells of Leydig, and those with this disturbance are quite similar in functional incapacity to a castrate but without the absence of the testes. Here there is complete functional loss of the sex principle later in life, so that the more marked manifestations of infantilism are not present.

The eunuchoid is so named from the similarity in form to the eunuch or castrate, and in addition to the retrogressive changes

in the secondary sex characteristics—avirilism, reduction of facial, axillary and pubic hair, genital atrophy, etc., there is an acquired corpulency due to the loss of the powerful oxidizing principle produced in the interstitial cells. A subnormal temperature is the rule in these individuals, and it has even been suggested that this common associate finding in senility (or presenility) is of gonad origin.

Eunuchoidism may be due to disease or be a spontaneous hormonically produced disorder, and it is accompanied by a loss of the factors dependent upon active sex-gland function—assertiveness, courage, animation and sexual power. The ergograph has been effectively used to demonstrate the actual loss of energy and power following disease or injury to the gonads, as well as to show the energizing influence of suitable organotherapy or the more recent work by Lydston and others with sex gland transplantation.

Functional Sexual Disturbances. Many a monograph has been written on this subject, and it is far too large to be considered fully here. Impotence, presenility and senile testicular insufficiency always have been a subject of perennial interest. From a diagnostic standpoint, the principal symptoms are lack of sexual desire and power and "sexual neurasthenia" with its innumerable manifestations. According to Williams, functional testicular disorders, especially on the side of deficiency, are known to cause general depression, hysteria, hypochondria, melancholia and also digestive disturbances.

It may be well to recall that the fundamental basis of modern organotherapy and the "fillip" which restarted an interest in the age-old study of organ medication was the use by Browne-Sequard of testicular extract on himself. The dynamogenic influence of this sort of treatment then, as now, is unquestioned; but for various reasons it has never assumed the importance that it really deserves. It is given some consideration elsewhere in the chapter entitled, "The Hormones in Impotence" (Sec. V, Chap. 12).

Senility and Presenility. According to Lorand, "A man is as old as his internal secretions," and the condition we call "age" is nothing but a gradual waning in the endocrine functions with the accompanying reduced cellular activity and unavoidable toxemia, which finally overburdens the body and allows the vital organs to peter out. The condition we call "senility" is merely old age, and "presenility" is a premature aging which may range from the remarkable condition known as progeria (infantile senility) to a premature loss of virility. This capacity, the maturity and strength of manhood, is bound up in the powers of procreation; and when this capacity wanes, whether from age or disease, senility exists—or avirilism. This is accompanied by

loss of strength, deficient oxidation, malnutrition, especially of the skin and appendages, and resulting in wrinkles, old appearance and the loss of hair and, above all, of the endocrine and spermatogenic functions of the testes. This is a natural consequence of the ravages of time, just as it is a premature consequence of the ravages of lust. In both instances, the essential sex glands are functionally inactive, and there is present the same hypogonadism that we find in the pathological conditions previously enumerated.

The diagnosis need not be discussed further, and its successful control through a mythical *"Elixir Vitae"* has been the goal of many from time immemorial and from Ponce de Leon to the present day. Hypogonadism may be amenable to organotherapy, even in elderly men, and the fundamental principle of homostimulation (see Sec. II, Chap. 2) holds good "in proportion to the responsiveness of the glands thus stimulated." It is a broader matter than the gonads alone, as the thyroid, pituitary and other endocrine glands all play their part. Senility, then, is hypocrinism rather than hypogonadism alone; and if we must treat it, it should be treated in the larger sense; and when organotherapy is in mind it should be preferably *pluriglandular therapy.*

Undoubtedly there is such a condition as hypergonadism; but in most cases we have to meet, the origin is psychic and usually beyond the control of ordinary medical treatment. From a diagnostic standpoint, it is not difficult to determine.

SECTION IV. CHAPTER 8

THE DIAGNOSIS OF OVARIAN DYSCRINISM

The ovaries produce at least two distinct internal secretions, one from the corpora lutea and the other from the interstitial cells or stroma. The differentiation of the hormonic value of these substances is difficult, but, broadly speaking, the luteal hormone is chiefly concerned with the determination and production of menstruation and probably the growth of the sex organs, while on the other hand the stromal hormone is chiefly concerned in the regulation of the nutrition of the uterus and is believed to exert a hemostatic action upon the menses. Some believe that the luteal hormone also sensitizes the uterus to prepare it for pregnancy and the development of the placenta. It is suggested that these two hormones, acting in alternation, bring about the entire phenomenon of menstruation.

The biochemical basis of femininity is much more important than either the psychological basis or that dependent upon the

nervous system. The hormones transcend in importance all other factors in the regulation of the chemistry of the body and, therefore, the chemistry of the reproductive organs. Hence, derangements in the endocrine glands, particularly the gonads, spells disturbed metabolism, altered nutrition and modified sex conditions. Most certainly the ovaries have much more to do with remote non-sexual factors than is usually believed; and while it may not be known to which portion of the organ the effects may be credited, it is certain that the ovaries are definitely concerned in the subtleties of cellular chemistry and have much to do with the maintenance of the calcium balance.

The Influence of the Associated Glands. The fact that the ovarian internal secretions are so intimately connected with those of other glands, notably the thyroid and pituitary, makes it rather difficult to set down accurately the results of ovarian dysfunction since the symptoms may not necessarily be purely ovarian but rather due to a pluriglandular manifestation which includes factors not of ovarian origin at all. For instance, according to Osborne, a woman castrated during menstrual life generally adds weight, not only because of the cessation of the loss of blood, but also because of the loss of the ovarian secretion and *"of the coincident lessening of thyroid secretion and perhaps of pituitary secretion."* The supreme importance of these relations is emphasized in another quotation from the same authority (*N. Y. Med. Jour.*, Sept., 1918): "The thyroid is typically a female gland, entering constantly into the woman's sexual life. Menstruation cannot possibly occur without the activity of the thyroid. Too much thyroid secretion may cause profuse or too frequent menstruation. The thyroid hypersecretes at each menstrual epoch and during pregnancy, and many disturbances of the menopause are due to too much or too little thyroid secretion. . . . All through female life, the thyroid secretion is of constant importance, and normal ovarian and uterine functions cannot occur without normal thyroid function. In female cretins, the genital organs may develop, but they do not function."

Another phase of the thyro-ovarian relationship must be mentioned, under the circumstances. The ovarian secretion reciprocally stimulates the thyroid, and at the change of life the absence of hormone stimulation from the ovaries may cause a thyroid insufficiency, with the result that the woman adds weight more or less rapidly, the skin becomes dry, she may be sleepy and more or less mentally apathetic, and in general she shows the signs of myxedema. According to Osborne, "this (menopause) is a period of life when myxedema is most frequent, by far the majority of all non-operative myxedematous cases occurring in women and in the decade of forty to fifty." Hence it can be seen, both from the standpoint of cause as well as of effect,

that ovarian insufficiency is so definitely connected with the thyroid function that the symptoms are really also the symptoms of thyroid insufficiency, and vice versa.

From the standpoint of diagnostic endocrinology, the ovaries are subject to three forms of functional disorder: (1) deficient secretion, (2) excessive secretion, and (3) perverted secretion. The results of these, limited as far as possible to the ovaries and not to pluriglandular syndromes in which the ovaries play a part, will be considered briefly from the diagnostic standpoint.

Symptoms of Ovarian Insufficiency. The outstanding manifestation of hypoovarism is amenorrhea in varying degrees from a complete absence of the menses, through irregular menstruation to delayed or scanty menstruation, frigidity, sexual apathy and sterility. Equally important is dysmenorrhea in its various manifestations. The underlying disorder may be early and spontaneous in origin, or it may be a later, acquired condition; i. e., the change may be initiated sufficiently early to prevent the normal development and growth dependent thereon, or, on the other hand, ovarian disease may supervene after maturity with an obviously modified train of results. The former condition naturally implies a wider and more fundamental symptomatology, for the changes of puberty are purely of endocrine origin and the ovareis are among the principal agencies in bringing them about. The results of early ovarian insufficiency are combined and generally known as "infantilism." The usual findings include delayed or arrested growth of the body as a whole and of the reproductive organs in particular. The breasts may be small and undeveloped, though not infrequently this does not appear to be the case, especially when there is plenty of fat in the tissues. The hips are narrow. The pubic and axillary hair is scanty or absent; and the psychic and sensory evidences of sex are diminished in degree or entirely absent.

The later onset of ovarian insufficiency is not accompanied by such well marked evidences, at least as far as physical development is concerned, for obvious reasons; but the functional changes are usually clearly discernible. Since the growth of the myometrium and, in fact, the pelvic circulation and reproductive development are under hormone control, in cases of ovarian insufficiency the uterus may be expected to be infantile (or "senile") and the adnexa undeveloped or atrophied. Where this is acquired later in life, genital atrophy is to be seen as a shrinking of the internal and external genitalia. The labia majora diminish in size, while the labia minora are slender and insignificant and may disappear entirely. The introitus narrows and tends to become valve-like, and the modified vaginal membrane is thin, pale and mottled, later becoming tough and unyielding. The vagina contracts and obstructing bands may be formed, while the cervix shrinks and its lumen tends to close.

Typical Functional Ovarian Insufficiency. A more or less typical case of deficient ovarian functioning may be outlined: The patient complains of uncomfortable sensations, such as pelvic heaviness, vague nervous manifestations and a feeling of general malaise of varying degree for a longer or shorter time prior to each expected menstruation. Delay is the rule. Irregularity of onset and a scant flow are customary. During the "over" period she may and indeed often does suffer from severe colds, an old tonsillitis lights up, headaches of quite decided severity are common, boils or acne are sometimes found and, in fact, the patient is so tired and below par at that time that during it any latent condition may become aggravated because of the temporarily lowered resistance. When the menses do show up and get properly started, these troubles begin to disappear—until the next premenstrual delay. And so on. The delayed menstruation favors a condition of neurasthenia and worry which adds to the aggravation all around.

It is easy to see that neuroses are common in those suffering from dysovarism. Many sympathetic nervous disorders, well-defined as well as vague, have a large ovarian element in their make-up. Many cases called "neurasthenia" and many "reflex" mental and physical ills are connected in some direct or remote way with the mensual ovarian function. Occasionally these develop into psychoses, which may or may not respond to organotherapy. The fact that they are related in some way to ovarian physiology (or pathology), that they are influenced by conditions involving menstruation, intercourse, pregnancy or psycho-sexual matters should be proof enough. The best kind of conviction, however, comes from developing a supposition into a reality by initiating the right kind of treatment—in this instance, in my estimation, pluriglandular therapy—and controlling the manifestations, a thing that has been done times without number.

Menopausal Difficulties. When hormone production ceases at the "change of life," the delicate hormone balance, the mechanism of which has depended upon ovarian hormone activity for approximately thirty years, sometimes is sadly deranged, causing considerable disturbance in the work of the other ductless glands. The extent of this trouble depends very largely (1) upon the previous ovarian hormone production, and a person who had been accustomed to quite considerable ovarian activity might react less favorably than where this activity had been less; (2) the rapidity of the completion of this function (a sudden menopause, like the "surgical menopause," is likely to be more severe than when the transition is more gradual), and (3) the sensitiveness of the associated glands, especially, in my estimation, the adrenal glands, which, it will be recalled, are unusually sensitive to toxemia, acidosis and emotional factors.

The organic changes are too well known to require reiteration

here and include most of the retrograde anatomical changes previously mentioned. The chief symptoms of this condition are of a circulatory character, due in all probability to the indirect influences upon the adrenal glands. Reflex troubles are often found, the most common of which is headache, probably of circulatory origin, although more than one case of post-climacteric headache has been known to be due to pituitary dysfunction, resulting, in all probability, from an attempt of the pituitary gland to make up for the ovarian deficiency—a "friendly" activity which is not always best for the patient. Flashes of heat, fleeting and indefinite pains, sensory disturbances in various localities, pelvic fullness due to congestion with frequent periods of menorrhagia, sympathetic irritability, on the one hand, or melancholia and depression, on the other, make up a symptom-complex which is often called neurasthenia but which is nothing in the world but dyscrinism—a disordered function of the glands of internal secretion due to the derangement of the balance between the ovaries and the other glands.

Functional Sterility. With the changes enumerated above, one would expect to find sterility, and this, of course, is the rule at the menopause. Indeed, the capacity to house an impregnated ovum has much to do with the endocrine glands, and many cases of presumably normal ovulation, with or without menstrual difficulties, are sterile because the ovum is lost. Indeed, this form of sterility may be the only sign of ovarian insufficiency, and there certainly must be many early abortions in which the cause is not so much defective ovulation (syphilis having been ruled out) as a difficulty in the proper implantation of an apparently normal embryo, a function which is now conceded to be made possible through hormone influences and which, fortunately indeed, occasionally may be remedied by suitable organotherapy.

The endocrine aspect of sterility and the organotherapeutic remedying of this condition are subjects which are being given close attention at this time, and within the last year several very comprehensive articles have been written, perhaps the most interesting of which is by S. W. Bandler, of New York.

From my own standpoint, sterility, even of a most persistent character, is not nearly such an impossible condition as has been supposed. I have personally seen a number of cases in which every anatomical feature was normal—the chemistry of the vaginal secretion was ruled out as a factor—but there was a subtle dysthyroidism which was only discovered by the use of my thyroid function test (see Sec. IV, Chap. 4), and upon the initiation of a comparatively short course of suitable organotherapy, the desired impregnation occurred. With this thought in mind, it may be well to recall some things that have already been said about the thyroid, pituitary and ovarian functions. Myxedema and the less serious forms of thyroid insufficiency

spell ovarian insufficiency, amenorrhea—and sterility. The typical pelvic findings in hypopituitarism are a functional ovarian insufficiency and, later, atrophy of the whole genital system. There is also a pituitary element in sterility. Possibly other glands are also involved, but it is certainly true that the consideration of the "endocrine trinity of sex," the ovary, thyroid and pituitary glands, opens up a fertile field for the clinical treatment of many functional pelvic difficulties, including sterility, and attention is called to the chapter on "The Treatment of Functional Ovarian Disorders" (Sec. V, Chap. 3), in which reference is made to two formulas, the one No. 4, *Caps. Thyro-Ovarian Co.* for the regulation of the ordinary disturbances of ovarian function, and S. F. No. 73, *Caps. Gonad-Ovarian Co.* (containing anterior pituitary substance in addition) for the more definite cases of sterility and sexual apathy, including those in which ovarian therapy and the thyro-ovarian formula have been tried for some months without a satisfactory outcome.

Over-secretion of the Ovaries. Excessive ovarian activity is not nearly so frequent as hypo-ovarism. Rarely in early life it may accompany pituitary disease, abnormal thymus atrophy or a pineal tumor, and as a result of the dyscrinism the ovaries may commence to functionate very early or abnormally. Cases are on record where the evidences of puberty were present at five years; and, from the standpoint of fecundity while procreation may not have been possible, at least such cases were rightly classed as "precocious." For reasons that may not be always clear, psychic, endocrine or organic, the ovaries may function excessively, as a result of which those factors dependent upon ovarian function are increased, including sexuality, which may develop into all kinds of sexual perversion, and menorrhagia. This latter may be represented by too frequent menstruation or by an excessive flow at proper intervals. There may be varying degrees of pelvic sensitiveness and pain, with a sense of uncomfortable fullness in the lower abdomen due to congestion. This same circulatory derangement results in irritation of the external genitalia, and the sympathetic balance may be so badly disturbed that hysteria may be directly due to this disturbance.

The adrenal glands may be so excessively stimulated by this abnormal production of the ovarian hormone that they may be depleted, and following the condition of adrenal irritability and sympatheticotonus there may be long periods of adynamia and asthenia so common in certain ovarian cases. It should be remarked in passing that numerous other circumstances may be the cause of adrenal depletion; and the consequent asthenia, while accompanying other evidences of hyperovarism, really may be due to other remote causes. Functional hyperovarism is practically never existent without associated sexual neuroses, and it may include masturbation and nymphomania, even growing into

"sexual insanity." Several years ago, the writer suggested a therapeutic-diagnostic test which is well worth trying in hyperovarism. Functional menorrhagia and other conditions purely due to ovarian excess (not to new growths or to mechanical causes) are often modified by mammary organotherapy. Five to ten grains of desiccated mammary gland given three times a day before meals have controlled the hemorrhage and pelvic uncomfortableness very nicely. At the same time this assists in establishing the functional basis of the disorder. (Parenthetically the internal secretion of the mammary glands exerts an antagonistic action over that of the ovaries (see Sec. V, Chap. 14), as does that of the pancreas over the secretion of the adrenal medulla, and vice versa.)

Osteomalacia an Ovarian Symptom. One of the chemical results of hyperovarism is especially noticeable in osteomalacia. This lack of lime and softening of the bones is now known to be intimately connected with the glands of internal secretion and particularly the ovaries. Osteomalacia may be brought about directly by ovarian excess (and be remedied very largely by removal of a portion of the hyperactive glands just as the thyroid is removed, in part, in hyperthyroidism, etc.). In these cases, the disordered calcium metabolism is due probably to the abnormal excretion of lime brought about by the undue ovarian stimuli. Blair Bell has shown by numerous experiments that the ovaries are an important factor in the regulation of the power of the organism to appropriate calcium; and the clinical experiences with osteomalacia seem to prove his contention. This condition is not usual in non-pregnant women as they do not have the great need for lime that is present during pregnancy; but since child-bearing causes a large demand for extra lime, softening of the bones may occur and is not uncommon in Italy, Austria and India. At one time, osteomalacia was routinely treated by oophorectomy, but since Bossi, in 1907, first suggested the administration of an antagonizing hormone instead of ovarian removal, adrenal substance has been given with many resulting cures. More recently Blair Bell has directed the treatment of a series of cases in India, at long range, and at his suggestion the posterior pituitary principle has been given in osteomalacia with distinct benefit in a number of cases. This seems to indicate that osteomalacia is likely a pluriglandular disorder, the hyperovarism being coupled with hypoadrenia or hypopituitarism. This is undoubtedly the case and indicates, at least, a prospective line of treatment of hyperovarism where ordinary treatment is unavailing and operation inadvisable.

The Causes of Ovarian Excess. The first cause of hyperovarism is functional irritability due to the circulatory derangement accompanying pelvic inflammation or malposition of the uterus. Another common cause is connected with hygienic con-

ditions of a personal nature, involving associations, reading and various sex circumstances. These two factors, mechanical and psychic, induce a condition of circulatory stasis which is equally the result of infections, uterine subinvolution and malpositions. This stasis is a common cause of ovarian disease which is first functional and later organic.

The Ovarian Element in Fibroids. A number of years ago, surgical removal of the ovaries was recommended for the control of uterine fibroids and the accompanying menorrhagia. It is well known that the menopause frequently alters the symptoms of fibroid growths and causes a cessation of their growth or a reduction in size. Ovarian antagonism by the X-ray is a frequent recourse in fibroid menorrhagia; likewise, organotherapy opposed to ovarian hormone function reduces the symptoms.

All of these facts lend weight to the belief that uterine fibroids are possibly the result of hyperovarism, and, among others, Briggs of Sacramento believes that the exciting cause of these new growths and the accompanying hemorrhages is uterine hyperemia of ovarian origin and that the antagonistic effect of the mammary principle is helpful because of its anti-ovarian influence. Briggs reports a number of clinical experiences to establish his theory and states that in "a large majority of cases receiving mammary extract, the menorrhagia is effectively controlled and under its continued use large uterine fibroids often disappear, even during the early reproductive period." The mammary hormone probably antagonizes the follicular (stromal) hormone or inhibits its production and thus moderates or prevents an excessive menstrual molimen and its consequent hyperemia, menorrhagia and local nutritive disturbances. The effective dosage therefore would seem to depend on the degree of excessive ovarian activity—the greater this functional activity the larger the quantity of mammary extract required to inhibit or antagonize it.

This conception of the cause and treatment of fibroids has been successfully carried out by many physicians (see Sec. V, Chap. 14, "Mammary Extract in Therapeutics"), and the use of the S. F. No. 40, *Caps. Mamma-Pituitary Co.*, is recommended because each of the ingredients favors uterine depletion and encourages pelvic tone, while the mammary extract is a direct "anti-ovarian" remedy.

Organic Ovarian Disease. Local structural changes in the ovaries themselves are very numerous and they really form a third class of cases of ovarian dysfunction, for the excessive endocrine activity is not so much an increase in the normal production of the ovarian hormones as the actual production of aberrant chemical substances from new growths or cysts in the ovaries. The frequency of ovarian tumors is responsible for this, and the condition is differentiable from hyperovarism and the

clinical findings are irregular since this disorder may be accompanied by periods of ovarian excess or insufficiency. Occasionally there is produced in the ovarian tissue (either in the normal interstitial or luteal cells, or in those of the new growth) a toxic hormone of extreme virulence, and in comparatively recent German literature the term "ovarian poisoning" is found, denoting a vicious activity of diseased ovarian tissue with serious remote effects due to the poison produced there and secreted directly into the blood stream as are practically all the hormone-bearing internal secretions. The treatment, of course, involves the removal of the offending tissue.

Dysovarism may be the cause of alternate periods of amenorrhea and menorrhagia. Dysmenorrhea is the rule. Neurotic manifestations are quite usual, and some have reported insanity as one of the possible results of this variety of ovarian derangement incidentally explaining some remarkable "cures" of insanity following surgery of the ovaries. Under certain circumstances an abnormal menopause virtually develops into a minor form of dysovarism, the varying symptoms being due to irregular periods of differing ovarian activity.

The most common symptoms of dysovarism are pain in the pelvis and severe asthenia. The extreme prostration and weakness is doubtless due to a superinduced hypoadrenia, and may be the outstanding feature of a case. In most cases, on bimanual palpation the offending organ or organs frequently will be found to be nodular, irregular, enlarged and tender. Here again surgery is the proper remedial procedure.

A side to this subject which is perhaps more practical in its application, is given consideration in the chapter entitled, "The Treatment of Functional Ovarian Disorders," which constitutes Chapter 3 of Section V.

SECTION IV. CHAPTER 9

THE DISORDERS OF THE THYMUS

Disorders of the thymus gland are not common, though they are undoubtedly more frequent than is supposed. There always has seemed to be an element of mystery about this gland, due possibly to the strangeness and suddenness of deaths of thymic origin. However, this is being replaced, and we are now able to understand the thymus better than we did a few years ago.

As with the other ductless glands, we may find a cellular enlargement of the thymus with local symptoms due to pressure; or, on the other hand, there may be a change in the functional

activities of the gland with varying effects upon the body as a whole. It is not yet generally conceded that the thymus is really a gland of internal secretion, although it influences metabolism and also the work of the other ductless glands in a manner very similar to other known endocrine glands.

It has been suggested that the principal function of the thymus is to produce lymphocytes, and Sajous, of Philadelphia, believes that any effects that it may exert upon metabolism, positive or negative, are due to these cells or their contents. Of course, it is quite possible that these blood cells carry within themselves certain chemical substances which are very closely allied to hormones, if not actually such.

Physiological Considerations. Most authorities consider the thymus as a temporary organ which reaches its height of development about the age of two, and retrogrades slowly until puberty, at which time it is supposed to disappear, though this opinion is not unanimous. Proof that the thymus is not a lymphoid organ alone is found in the intimate relation between the thymus and the metabolism of the mineral salts, especially of calcium and phosphorus. For when there is early or experimental thymus dysfunction the chief organs to suffer from the resultant chemical changes are the bones, muscles and, perhaps, the nerves, in the order named.

There is an abundance of evidence connecting the activities of the thymus with those of the gonads. It seems that the thymus antagonizes the action of the sex glands, and that increased thymus function, especially during the period of development, causes deficient reproductive development; while, on the other hand, deficient thymus activity may cause an increase in the growth and function of the gonads. At least we know that if the thymus does not retrograde in the usual manner at puberty there likely may be evidences of defective sexual development, and from this the conclusion is drawn that the study of the thymus should be a part of the study of all cases of deficient gonad function or development.

Another important clinical fact which indicates another physiologic intimacy of the thymus is found in its relation to idiocy in children. It has been remarked that a large percentage of idiotic children have no thymus at all. Morel reports that of over four hundred idiotic children with normal thyroids coming to autopsy, over 75% possessed no thymus. In passing it is interesting to note that Klose has experimentally shown that thymectomy in dogs is followed by a gradual change in the mental powers until a condition which he terms *idiotia thymopriva* is present. While this does not necessarily prove that athymia is the cause of idiocy, it is at least a very suggestive finding and one which has been well established by many investigators.

Thymus Insufficiency. Experimental proof is at hand to show that the removal of the thymus from animals causes a decided reduction of growth—dwarfism. It is not improper to presume that this holds good with children. At least there is a probable thymic element in dwarfism, and support of this is found in several communications which report benefit following thymus feeding in certain cases where weight is low and the height reduced.

Certain nutritional disorders in children, notably marasmus, are quite commonly associated with thymic atrophy, and some interesting clinical proof of this is available. Deficient children, especially when there are disturbances in bone growth and development, should always be considered from the thymus aspect until definitely proved not to be suffering from hypothymism. Parenthetically my pluriglandular formula No. 2, *Caps. Antero-Pituitary Co.*, which is recommended in the treatment of defective children contains an effective dose of thymus substance. (See Sec. V, Chap. 7.)

Naturally hypothymism is not to be expected in adults for the gland normally becomes inactive at or near puberty. However individuals with thymus dyscrasias in childhood may retain certain chemico-nutritional disorders as a result of the previous disordered function of this gland.

The blood changes are not characteristic; but one frequently finds hypothymism accompanied by anemia and especially lymphocythemia. Reduced coagulability is also common and frequent bleeding at the nose may be the first indication of thymus disorder. Still another incidental defect has been connected with dysthymism. Browning states that there is a relationship between the thymus gland and stammering. While all cases with an enlarged thymus do not stutter, all stutterers will be found to have an enlarged gland. This is denied by some, but is worth remembering. After all, success in the detection and treatment of ductless glandular disorders is attained by noting insignificant things.

One frequently notes a peculiar condition of hairlessness (especially of the head and face), and a yellowish, parchment-like skin in pluriglandular dyscrasias in which the thymus element is or has been prominent. Parenthetically it may be well to remark that Sajous suggests that the rare condition known as progeria or premature senility (in children), is really due to thymus disease.

Some of the findings in experimental and clinical work are sometimes contradictory, and the reason for this is due to the fact that the endocrine organs are so intimately connected with one another. At one time a certain hormone seems to be in the ascendency whereas at another it is deficient. As an instance of this a case of presumed hypothymism with retarded growth

and sexual development was treated with thymus substance for some months with a remarkable increase in height and general progress, though it must be recalled that theoretically the removal of the antagonism of the thymus (as in hypothymism), should favor functional gonad activity and the developmental and other results thereof.

Hyperthymism. Hyperthymism is not a common or easily diagnosed condition. It is rarely found unaccompanied by other ductless glandular disorders, indeed it is a disorder which one should be ready to look for mainly in connection with certain forms of thyroid excess. A number of reports indicate that one should carefully look for an enlarged thymus and evidences of its excessive activity in every case of Graves's disease, and particularly before surgical intervention is undertaken. After a careful search both of the literature and numerous unpublished hospital records, Matti collated 133 cases of sudden death in hyperthyroidism in which a post mortem examination had been held and in 98 cases, or 74%, a hyperplastic thymus was found. Such records emphasize the advice just given regarding the relation of thymus disorder with Graves's disease.

A number of deaths have followed thyroid operations, due to thymus complications. Not a few times a share, at least, of the heart and nervous symptoms attributed to hyperthyroidism has been due to a concomitant hyperthymism. In this connection it must be emphasized that while an enlarged thymus may be usual in such cases, there is no doubt that the degree of thymotoxemia may have little to do with the size of the gland.

Experimentally and clinically excessive thymus function is accompanied by severe general nervousness, tremor and a rapid irregular pulse. Thymotoxemia of this character may be amenable to roentgenization of the thymus area.

There is a somewhat rare thymus type of adiposity which is usually accompanied by lymphatic tendencies, and in which one often may find a well defined thymus area on X-ray examination. In such cases myasthenia is persistent and may disappear after suitable treatment—roentgen or surgical.

In cases with thymus disorder one usually will find a considerable increase in the number of lymphocytes in the differential blood count, and this procedure is recommended not merely when thymus disease is suspected, but in the routine clinical diagnosis of Graves's disease.

According to Paltauf the characteristic features of hyperthymism are: (1) Hyperplasia of the various groups of lymph glands, tonsils, spleen, and, of course, the thymus itself (see status thymo-lymphaticus); (2) Lymphocytosis, the count being increased to 50% or more (i. e., increased 100% or more); (3) Cardio-aortic aplasia; (4) Maldevelopment of the genital glands and their adnexa; and (5) A pale, badly nourished skin with

scanty hair and an exaggerated *panniculus adiposus*. It is fair to add that one rarely finds all these in a single case.

Diagnostic Points in Thymus Cases. Attention already has been called to the value of the Roentgen ray in the diagnosis of thymus disorder. An enlarged thymus occasionally may be percussed as a triangular area of dullness under the manubrium of the sternum, in some cases extending outward on either side a short distance. This area of dullness may move slightly upward on extending the neck by drawing the head well back. The base of this triangle is between the sternal ends of the clavicles, and the apex between the junctions of the sternum with the second and third ribs. Halstead has noticed that downward pressure on the sternum may produce a sense of suffocation in cases of this character, which differs considerably from the normal.

It should be recalled that there is such a condition as a substernal goiter or an intrathoracic thyroid; but this may be differentiated by the somewhat higher position of the enlargement and the fact that it moves with the trachea in the act of swallowing.

Hoxie has described a symptom complex in which an enlarged thymus is accompanied by shortness of breath and discomfort in the thorax, and extreme muscular weakness. In several cases reported the asthenia was quite the most prominent subjective finding. This is of special interest, as there seems to be clinical evidence that myasthenia gravis is in some way connected with the thymus. Tom Williams has reported a case of a man with this disease who was apparently cured by the administration of thymus substance.

Thymus Hyperplasia in Children. We have already discussed thymus enlargement and hyperactivity; but thymus hyperplasia in children deserves mention by itself. It seems to be a somewhat different clinical entity not uncommonly found in infants and children and, unfortunately, too often only at the autopsy table. Many times this hyperplasia causes no well defined symptoms and is altogether latent until sudden death, the so-called "*mors thymica*," is the first indication that something was wrong.

In infants, where an enlarged thymus is present, the initiation of breathing may be a prolonged and difficult matter. The cyanosis present at birth may persist and the breathing may be difficult and stridorous. In such cases the outcome is often fatal after a few hours or days.

Dyspnea in children is probably the most marked symptom of thymus hyperplasia, and its presence should always cause a careful search for other associated findings. It may vary in degree, depending upon the pressure, from an insignificant stridor worse on stretching the neck or drawing back the head, to a serious and alarming air hunger.

In such cases the general health is poor. The skin has a pasty,

badly nourished appearance, not unlike that of cretinism. There may be vague respiratory symptoms due to tracheostenosis, which later may develop into a peculiar harsh and intermittent cough which is sometimes erroneously called a "tooth" cough, a "stomach" cough or, for lack of a better name a "nervous cough." This cough occasionally may be short and dry during the day and considerably worse at night. It is possible that the cough may not be due to pressure on the air passages, but to irritation of either the recurrent laryngeal or vagus nerves, although tracheal stenosis is the most usual cause.

Status Thymo-Lymphaticus. This disorder differs somewhat from thymus hyperplasia since it is evidently an acquired condition and is more frequently observed in older children and young adults. It is a more complex condition, the hypertrophic changes in the thymus being accompanied by a general enlargement of the bronchial, mesenteric and other lymphatic glands. According to Hart, the existence of a true status lymphaticus has not yet been proved with absolute certainty. To him it appears that the swelling of the lymphatic apparatus represents a tissue reaction dependent on the thymus and which may show itself also in the lymphoid components of the thymus itself.

Adenoids and enlarged tonsils are usual, hence cases with a well marked adenoid facies and other evidences of lymphatic enlargement should be studied as likely cases of status lymphaticus and the thymus should be sought for and, if possible, measured. According to Bierring and others, unexplicable deafness has been found in a number of cases.

In the past status thymo-lymphaticus commonly has been diagnosed after sudden and unexplained death. We are now better posted on the symptomatology of thymus dyscrasias, and with increasing frequency this condition is detected before extreme results show themselves and in time to treat the thymus with the Roentgen ray.

Individuals with status thymo-lymphaticus usually are of the flabby, semi-obese type, with a peculiar pasty appearance of the skin of the exposed parts. Pigmentation is occasionally seen, especially in cases of Graves's disease with thymus involvement. Incidentally the records of the pathological department of the Johns Hopkins Hospital indicate that adrenal atrophy (and presumably adrenal insufficiency) is common in cases dying from status thymo-lymphaticus. Asthenia is a usual symptom and sometimes overshadows the other subjective symptoms, and, presumably, it is of adrenal origin. Such cases often suffer from severe metabolic disorders with an intoxication which is quite probably of endocrine origin.

Quite often the development of the bones is disturbed, the growth of the extremities being stunted and a condition of softening quite similar to osteomalacia has been attributed to

thymus disorder. At least derangements of the calcium metabolism are quite usual in thymus disease.

The circulatory system is ineffective due to hypoplastic changes in the heart and great vessels. As a result of these organic changes resistance to disease is low, "the constitution is poor" and trivial things may produce sudden death. In young individuals the abdomen frequently assumes that type known as "pot belly" and there is an important clinical connection between thymus disorder and rickets.

Thymic Asthma. The dyspnea of thymic origin has somewhat erroneously acquired the name "thymic asthma." This is really a form of inspiratory dyspnea due most usually to tracheostenosis caused by pressure by an enlarged thymus. It is only one of a series of symptoms of thymus hyperplasia and is not a distinct entity, nor is it amenable to treatment different from that which is directed at the removal of the thymus or, at least, the pressure that it exerts upon the structures adjacent to it.

SECTION IV. CHAPTER 10

DISTURBANCES OF THE PARATHYROID GLANDS

The parathyroid glands, sometimes called "the epithelial bodies," were discovered in 1880 but their significance was not hinted at until 1891 when Gley, of Paris, connected them with tetany. Since then much work has been done to establish the fact that the parathyroids are definite endocrine organs.

Parathyroid Physiology. The diagnosis of parathyroid dysfunction necessarily presupposes some information regarding their physiological effect upon the organism. Briefly, it may be said that while complete information about the parathyroid functions is not yet available, it is evident that the parathyroids (1) exert a control upon calcium metabolism and (2) have an antitoxic action, the chief purpose of which is the destruction of "substances which have a predilection for influencing nervous tissue." The parathyroids are quite independent from the thyroid, both in origin, histology and function. This does not prevent a direct or indirect relation between the functions of the two systems. It is believed that parathyroid insufficiency, to some extent, checks the function of the thyroid.

Experimental removal of the parathyroids usually causes early death, preceded by a neuro-muscular symptom-complex described under the name of tetany, which is accompanied by a marked loss

of calcium, a fact which has been emphasized clinically by the excellent results of MacCallum, of New York, and others from the administration of calcium salts in the suppression of symptoms due to parathyroidectomy. An analysis of the cases reported indicates that the occurrence, intensity and course of postoperative tetany in man are dependent upon the parathyroid tissue that may be left.

The Symptomatology of Tetany. The principal symptoms of tetany, whether spontaneous or due to experimental parathyroid ablation, are very easily diagnosed. Intermittent tonic spasms of the voluntary muscles are the rule, especially in the extremities. The flexor groups of muscles are almost exclusively involved. Connected with these muscular symptoms are headache, asthenia, varying degrees of rigidity of the limbs, twitching and severe muscular pains. The contractions begin in the hands and later affect the feet, causing the muscles to become very hard to the touch and to oppose decided resistance to attempts to relax them. Fibrillary twitchings are sometimes seen. These experiences occur for varying lengths of time from a few minutes to several hours. Usually there are several attacks in the day. The patient is restless at night, and in severe cases, while consciousness is retained, extreme dyspnea may occur.

Several clinical tests are available, especially in the differentiation of mild and early tetany. The test suggested by Erb consists of the discovery of a marked irritability of the motor nerves, especially the ulnar, to galvanic stimuli. Very small amounts of electricity cause decided contractions, and this test should be made in all suspected parathyroid cases because of its sensitiveness and accuracy. Another common phenomenon, first noted by Trousseau, consists of the production of a tetanic spasm in a limb following compression of its main nerve trunks. Further, brief muscular twitchings in the face can be elicited in patients with tetany by gently tapping over the distribution of the facial nerve (Chvostek's Sign). All these tests, of course, are made between the spasms.

Another pathognomonic finding is a marked increase in guanidin and similar substances in the blood and urine, and it seems from the work of Noel Paton of Glasgow, Koch of Detroit, and others, that the conclusion is warranted that the parathyroids exert a destructive katabolic action upon guanidin and its precursors, for the presence of these substances and the results of their irritation of the body as a whole, and the nervous system especially, are very marked. The condition known as spasmophilia, an abnormal tendency to convulsions in infants and children, is thought to be of similar origin and also associated with undue calcium depletion.

There is such a thing as chronic tetany, in which occasional paroxysmal tonic contractions of muscle groups are found, to-

gether with paresthesias (usually in the hands and feet), hyperexcitability of certain nerves and trophic changes in the teeth, hair, nails and bones.

A Hypoparathyroid Syndrome. Parathyroid insufficiency does not necessarily involve a picture of tetany such as has been given. Hertz, of London, reports a case of hypoparathyroidism where extreme depression, nervousness and restlessness appeared suddenly. The patient was continually on the move and slept very little. He was exceedingly tremulous, had difficulty in writing, and there was a continuous fibrillary twitching of the eyelids, but no tetany. The appearance was quite similar to Graves's disease, except that the eyes were sunken instead of prominent, and no thyroid could be felt. The appetite increased, and he ate enormously but lost weight. He had some difficulty in swallowing, due to irregular spasmodic contraction of the esophagus, and some intestinal pain, probably due to a similar cause. There was palpitation, the pulse was continually about 120, and his face and neck were deeply flushed. In this particular case, parathyroid therapy caused an entire cure, and it is proper to say that various other methods of treatment directed previously at a presumed hyperthyroidism were useless. This is a rare case, but serves to emphasize the parathyroid symptoms.

Paralysis Agitans. It has been stated that various disorders associated with muscular tonicity and sympathetic irritability may be connected with the parathyroid glands, and the most thoroughly studied of these is Parkinson's disease, or paralysis agitans, in which it has been shown at autopsy that the parathyroids are quite commonly involved. Many clinical experiences with parathyroid feeding indicate a possibility of controlling the various well known manifestations of this disease. It is stated by Berkeley, of New York, that while parathyroid extract is not a "cure" for paralysis agitans, 60 to 70 per cent. of those who have given this remedy a fair trial for at least three to six months have been greatly benefited,* and in such patients the progress of the disease has been arrested, or very materially retarded. Based upon the same reasoning, it has been thought that eclampsia was connected with parathyroid insufficiency, but this is not well established. Another point of clinical interest is a special sensitiveness to neurostimulant drugs, such as strychnia, which has been linked up with hypoparathyroidism.

To sum up, the parathyroids evidently are intermittently con-

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* Berkeley gives parathyroid by mouth and hypodermically. Both are advisable for the first stage of the treatment; later oral administration is advisable. I have developed a Special Formula, No. 24, *Caps. Parathyroid Co.*, in which an average dose of parathyroid is supplemented by two known-to-synergize products, bile salts and spermin, the former to encourage hepatic activity and the latter to favor cell oxidation, two factors invariably involved in every case of this disease.

cerned in destroying certain wastes in the body, and their removal or insufficient function allow these products free play, with the resulting muscular and nervous irritation. It is well to add that certain digestive disturbances in children (gastric tetany) may cause a special toxemia which may result in dysfunction of these glands, and it has been noted that pregnancy puts an extra strain on the parathyroid functions, as evidenced by the occasional appearance of tetany in women and the common occurrence of tetany in partially parathyroidectomized pregnant animals. The chief clinical conclusion concerning the parathyroids is to connect them with conditions of marked neuro-muscular irritability.

The condition of hyperparathyroidism does not seem to have been given consideration, though theoretically it should be possible.

SECTION IV. CHAPTER 11

PANCREATIC ENDOCRINE DYSFUNCTION

The pancreas is an organ with both an internal and an external secretion. It is conclusively established that the internal secretion is the product of the islets of Langerhans, while the external secretion is produced in the cells constituting the walls of the acinous portions of the gland. Without a doubt, these two functions are related to one another, and conditions likely to cause pancreatic indigestion are equally likely to cause pancreatic dyscrinism.

Quite the most important disease due to disturbed internal secretory function of the pancreas is diabetes mellitus, and the amount of work done upon various experimental aspects of this subject is literally enormous. There are actually hundreds of papers on the subject, in a dozen languages; the amount of experimental work upon pancreectomized animals has been very great, and without taking much time or space, it may be said that the removal of the pancreas brings on immediate glycosuria, which may be mitigated or controlled by the successful implantation of pancreatic tissue and, quite often, by the administration of a preparation of the pancreas rich in its internal secretory product.

The Control of Sugar Mobilization. The pancreas produces a hormone, occasionally called the Langerhansian hormone, which von Noorden, of Frankfort, calls "the brake to the sugar factory." This has been called by Lepine, of Lyons, an anti-hormone, for indeed the chief function of the pancreatic internal secretion is not to "arouse or set in motion" but to regulate the mobilization of sugar, a function which is under the control of

the adrenal principle to which the pancreatic hormone is the direct antagonist. As a matter of fact, pancreatic diabetes, so-called, is in part at least a condition of adrenal sensitization due to the removal of part or all of the antagonizing hormone influences of the pancreas, and it is very probable that the initial disturbances of the digestive functions of this gland is responsible for the development of the diabetes, for diabetes is essentially a disease of those with overworked digestive organs.

In the experimental work upon various phases of the pancreas-diabetes question, it was discovered that the pancreas exerts quite a marked influence upon blood pressure, the general tendency being to reduce it, probably by its capacity to antagonize abnormal activity upon the part of the adrenal glands. The fact that the blood pressure is often very high in diabetes (pancreas insufficiency) tends to confirm this. It will be recalled that adrenin, the adrenal medullary principle, is a permanent factor in the maintenance of the normal blood pressure, and it is presumed that conditions of adrenal irritability or abnormal activity are likely to be associated with an increased arterial tension. This works out clinically very nicely, and it is a pleasure to be able to say that an organotherapeutic deduction has been made from these principles which is enabling us to reduce high blood pressure through the use of certain glandular combinations containing desiccated pancreatic substance. (See the chapter entitled "Reducing High Blood Pressure," Sec. IV, Chap. 10.)

The Pancreas and Immunity. Still another very important function of the pancreas concerns the resistance of the body to disease. Evidently, the pancreas exerts a well defined control over the immunizing powers of the body. Some years ago, I went into the study of this subject quite carefully and wrote a paper for *The Practitioner* (London), in which I showed that pancreatic dysfunction should be considered in every case of serious infection. Attention was called to the fact that in the experimental ablation of the pancreas for the purpose of causing artificial diabetes in dogs, the animals died from sepsis unless a small abdominal graft was made to maintain the pancreas endocrine control and thereby tide the dog over the serious operation, after which the graft could be removed later from the abdominal wall. Further than this, it is clinically well known that persons with diabetes are prone to aggravating infective conditions, as boils, carbuncles and gangrene. This may be an explanation for many favorable reports in regard to the use of pancreatic preparations in tuberculosis and other conditions where the resistance-maintaining department is overworked or incompetent.

So far as is known, there is no well defined condition of pancreatic hyperfunction, although such a condition may be physiologically associated with hyperpituitarism (acromegaly), in which

it is known that there is a disturbance in the capacity of the organism to care for ingested sugars.

SECTION IV. CHAPTER 12

LABORATORY MEASURES IN DIAGNOSTIC ENDOCRINOLOGY

The majority of the measures which enable us to diagnose and understand endocrinopathies are largely based upon clinical observations rather than diagnostic tests, laboratory or otherwise. Yet, as we have developed our knowledge of the subject, various procedures of a laboratory nature have been mentioned as helpful and deserve consideration separately. The subject has been considered very fully by Rosenbloom, of Pittsburgh, in a series of papers published in the *Interstate Medical Journal* (1918, Nos. 10, 11 and 12), and a brief consideration of the most practical and useful of these tests, with a passing reference to those which cannot well be made use of in ordinary clinical practice, will constitute this chapter.

Tests for Hyperthyroidism. One of the most constant results of hyperthyroidism is a condition of sympatheticotonus (see also Sec. V, Chap. 18), in which it is found that there is a marked sensitiveness of the sympathetic and vasomotor nerve endings, so that very slight doses of the adrenal medullary principle are capable of causing a much more rapid and marked reaction than is usually the case. Several tests are based upon this phenomenon.

Loewi's Mydriasis Test. In his study of experimental diabetes in animals and later in diabetes mellitus, Loewi discovered that the installation of one or two drops of adrenalin chloride solution (1:1000) into the conjunctival sac will cause a pupillary dilation within half an hour, which reaches its maximum within an hour and lasts 10 to 18 hours. Associated with it is a marked diminution or total absence of convergence miosis, though the light reflex is preserved. This reaction is quite commonly found in pancreatic diabetes, and Loewi also suggested that this test might be helpful in latent hyperthyroidism on the basis that the hormones of the thyroid and adrenals are synergistic, both stimulating the sympathetic; hence in hyperthyroidism the sympathetic system would be in a state of increased irritability, and the dilator nerves to the iris (governed by the sympathetic) would respond abnormally to the introduced adrenalin. Quite a number have confirmed the value of this test, but some state that it is not in-

variably useful; at least, this test may be done as a routine with possible advantage, with practically no trouble, and without detriment.

Goetsch's Adrenalin Test. This test is also based upon the exaggerated sensitiveness to adrenal stimulation which results from thyroid irritability. Eight minims of a 1:1000 solution of adrenalin are diluted with an equal quantity of sterile water and injected hypodermically into the arm. Immediately there is formed an area of blanching around the point of injection, and about the margin of this usually a red areola gradually shading off into the surrounding tissue. In about half an hour the center of the white area becomes bluish gray to lavender, and at the end of about one and a half to two hours the red areola takes on the bluish or lavender color, while that in the center disappears. This lavender areola remains for about four hours from the time of injection and is the most characteristic part of the test. Accompanying the local reaction may be an increase in pulse rate with palpitation of the heart and a temporary exaggeration of the tremor and the nervous instability in general.

This adrenalin test has been used by Goetsch and Nicholson at the Trudeau Sanatorium (*Amer. Rev. Tuberculosis,* Apr., 1919) in the differentiation of early tuberculosis from hyperthyroidism. If the patient, following the injections as indicated, reacts with manifest symptoms of hyperthyroidism, Goetsch believes that a positive diagnosis of this condition is justified and it will give a positive reaction whether associated with tuberculosis or not. On the other hand, tuberculosis uncomplicated by hyperthyroidism does not react positively to adrenalin, and they feel that in a considerable number of borderline cases showing symptoms more or less characteristic of both conditions they can now pick out those with hyperthyroidism and treat them accordingly.

Harrower's Thyroid Function Test. The administration of step-ladder doses of thyroid extract, accompanied by careful study of the pulse prior to, during, and for two or more days after the use of this extract may cause a material change in the pulse rate, depending upon the apathy or sensitiveness of the thyroid. On the one hand, hypothyroidism may be easily discovered by a lack of any reaction while, on the other, the pulse chart in hyperthyroidism is quite typical. (This subject is discussed more fully and explanatory clinical charts are reproduced in the chapter, entitled "A Method of Testing Thyroid Function," Chapter 4 of this Section.)

The Respiratory Quotient. The increased metabolism of this disease can be measured by studying the products eliminated through the lungs by means of the clinical respiration apparatus of Benedict, or other similar apparatus, developed in the Nutrition Laboratory at Boston. This is a very complicated procedure, involving much expensive apparatus, which enables one to deter-

mine the oxygen consumption, as well as the carbon dioxide production, both of which are considerably increased in hyperthyroidism.

Abderhalden's Ferment Test. Lampé and others believed that the blood serum of patients with hyperthyroidism contain ferments which are specific for thyroid tissue by following the Abderhalden method, and this indeed may be true, but I have always felt that the technique of these sero-diagnostic tests was too complex for ordinary physicians, and even too much the subject of error in the hands of accomplished technicians.

Tests for Pituitary Dysfunction. Metabolism and the respiratory exchanges have been studied in hyperpituitarism, and in the somewhat rare uncomplicated cases there is no increase as in hyperthyroidism (q.v.), but, unfortunately, it is not usual to have a pure pituitary monoglandular disturbance.

Marie's Artificial Glycosuria Test. The famous French neurologist, Pierre Marie, who first described acromegaly, also showed that it is often accompanied by disturbances in the sugar tolerance. Based upon this, it is possible to produce a "provocative alimentary glycosuria" by the administration of various forms of sugar, as follows:

1. *The Sucrose Test.* One hundred and fifty to 200 grams of cane sugar syrup are given to the subject in the morning while fasting. The urine is collected every hour and tested for reduction by means of Fehling's or Benedict's solution. A reduction makes the test positive.

2. *The Glucose Test.* The patient takes in the morning before breakfast, on an empty stomach, 150 grams of pure dextrin-free glucose dissolved in 300 c.c. of water. One can allow fifteen minutes in which to drink this solution. The urine is collected every hour for ten hours and each specimen tested for sugar. The patient stays on a milk diet during this time. The presence of glucose in the urine renders the test positive if it is known that the patient does not present a condition of spontaneous glycosuria.

3. *The Levulose Test.* One hundred grams of levulose are given in the morning on an empty stomach and the urine examined every two hours for the presence of sugar. A reduction shows presence of lessened ability to use this sugar.

4. *The Galactose Test.* Thirty grams of galactose are given to the patient in the morning on an empty stomach and the urine collected every two hours for six hours. The presence or absence of galactose in the urine is determined by Fehling's or Benedict's solution.

Sugar Tolerance Estimation. In hypopituitarism, there is a very marked increase in sugar tolerance; and while the above tests are carried out in the same manner, the patient with hypopituitarism is capable of tolerating very much larger quantities

of the various sugars, and twice or three times the amounts just indicated can be taken without a trace of glycosuria. (See Chapter 6, Section IV.)

Tests for Adrenal Function. *Adrenal Sensitization.* The most satisfactory laboratory test consists in the administration of one or two milligrams of adrenalin chloride (approximately 18 minims of the standard 1:1000 solution contain one milligram) by hypodermic injection. In cases of adrenal irritability, or hyperadrenia, a temporary increase in the blood sugar begins in about half an hour, as estimated by any one of the several methods now in use, and even the glycosuria may last two to six hours.

The Oculocardiac Reflex. In 1908, an Italian physician named Dignani called attention to a noticeable change in the pulse rate following compression of the eyeballs. This reflex has been found to be exaggerated in epileptics, and the reaction is more marked the more frequent the seizures. This reflex seems to be lost very early in tabes and may eventually be of differential diagnostic value. According to Peterson, of Copenhagen, this reflex deserves great attention from a medical, as well as a neurologic point of view, and is largely valuable in the study of paroxysmal tachycardia, a condition evidently due to disturbed *sympatheticotonus*, a condition of sympathetic virilability commonly connected with dysadrenia. Accordingly to Lian, of Paris, pressure on the eyeballs seems to be the most potent means at our command to influence the vagus and thus indirectly control heart action, and he recommends the use of this reflex test, not merely for diagnostic purposes but as a therapeutic means of arresting paroxysmal tachycardia.

Sergent's White Adrenal Line. Emile Sergent, of Paris, has described this vasomotor phenomena as a test of well-defined hypoadrenia. He traces a geometrical figure on the skin of the abdomen—a rectangle, triangle, or cross—obviating confusion with lines caused by folds of the skin, etc. The rounded end of a fountain pen is advised for the tracing. The figure should be made by a simple superficial stroking; one must not bear down or scratch the abdomen. After half a minute a pale line or band begins to be noticed following the tracing. Gradually this becomes more and more distinct and white, at the same time becoming larger, so that eventually the line exceeds in size the actual area touched by the pen. This white line attains its maximum clearness in the course of about one minute, and persists for one, two, or even three minutes before being gradually obliterated. This constitutes the reaction in well-defined cases of adrenal insufficiency. Sergent considers his so-called *"ligne blanche surrènale"* as due to the hypotension brought about by the hypoadrenia. It is known that in arterial hypotension there is present a peripheral vasodilatation produced by a slight stimulation of the

skin. Vasoconstriction replaces the vasodilatation with the resulting white line.

Tests for Parathyroid Dysfunction. *Erb's Test.* The laboratory test for hypoparathyroidism, or tetany, suggested by Erb is probably the most dependable and uniform of all the clinical procedures in the study of this condition. Galvanic stimuli of the motor nerves, especially the ulnar nerve, which in ordinary individuals are inactive, cause decided contractions in tetany. A kathodal opening contraction below five milliamperes is particularly significant, and comparisons with normal individuals show that in tetany contracture follows exceedingly mild stimuli.

Tests for Pancreatic Insufficiency (Endocrine). The internal secretory function of the pancreas is well known to antagonize that of the adrenals and at the same time is intimately concerned in the metabolism of carbohydrates. Deficient pancreatic secretion is accompanied by glycosuria; hence the administration of sugar will aggravate this. This does not differentiate between hepatic or pancreatic insufficiency, but in the former instance, the administration of desiccated pancreas substance may aggravate the glycosuria, while the use of desiccated liver substance for a week or more would cause a considerable reduction in the elimination of sugar in the case that the hepatic element was not prominent.

The Cammidge Test ordinarily is considered to be a useful measure for discovering whether the balance between the pancreatic and adrenal secretion is disturbed and to what degree. It is a complicated laboratory procedure, the discussion of which is unwarranted here.

Loewi's Test for Pancreatic Diabetes. The test suggested by Loewi as a means of discovering pancreatic insufficiency in diabetes is identical with that already mentioned under the heading "hyperthyroidism" and consists of instilling one or two drops of adrenalin chloride solution into one eye. Garrod, of London, has found this test positive in all pancreatic cases but rarely in other cases. Murray, of Manchester, agrees with him but does not believe it is as useful in hyperthyroidism as in diabetes. In this instance, it is presumed that the dilation occurs because of the mutual stimulation of the sympathetic by the thyroid and adrenals, and since the pancreas definitely antagonizes the adrenals in normal physiology, the removal of this antagonism would naturally tend to an adrenal or sympathetic irritability and hence of the dilator fibers of the iris.

Clinical Test with Adrenalin. Individuals with pancreatic diabetes are unusually sensitive to adrenalin. It has been noted time and again that the use of adrenalin in nose and throat surgery in diabetics, for instance, causes a marked increase in the average sugar output; and while such experiences amount to a "therapeutic test," it is not advisable to administer adrenalin

products when the adrenals already are so thoroughly uncontrolled by the absence of the normal antagonism of the pancreas "antihormone."

The Thymus Gland. *Differential Blood Count.* The study of the relative leucocyte counts in individuals with a persistent thymus usually shows a lymphocytosis, the small lymphocytes being increased very markedly. Of course, there may be other causes for a lymphocytosis—tuberculosis, for example—but this serves as one small factor in building up the picture.

Fluoroscopy. A persistent thymus often may be seen with the fluoroscopic screen. There is an increased shadow in the area represented by the triangle, the base of which is just below the suprasternal notch and the apex of which reaches to the level of the aortic arch or approximately the junctions of the second and third ribs with the sternum. Often the shadow is especially noticeable on either side of the angles formed by the clavicles, sternum and upper ribs.

SECTION V

EVERYDAY ORGANOTHERAPY

From time to time, letters come to me which prompt me to prepare an explanation in print—to save duplication of effort and to conserve time. In this Section have been gathered various articles pertaining to practical phases of organotherapy which have been written in answer to correspondents or as copy for The Organotherapeutic Review. *The groundwork of several of these articles already has appeared in this journal and has been carefully edited and amplified for publication in this book. Others have been written especially so that prospective questions may be answered comprehensively and quickly by directing attention to them.*

SECTION V. CHAPTER I

ASTHENIA: THE COMMONEST SYMPTOM IN MEDICINE

Practically all individuals with overburdened systems, that is to say, the majority of the cases of chronic disease which are so very common, suffer from asthenia—loss of strength. In fact, asthenia is probably the commonest single symptom seen in medical practice. The so-called "fatigue syndrome"—in which the patient tires too easily and too early, in which not only is there muscular tiredness, but initiative is lost and mental capacity is dulled—is one of the most important manifestations in the course of chronic toxemias.

As a matter of fact, asthenia is really another name for cellular intoxication—the muscles after work are tired because of the excess of intracellular wastes which have been produced in a quantity sufficient to overburden the usual means of elimination as well as all other mechanisms that are influenced by such toxins. The treatment is rest or refraining from all work and activity, during which time the poisons ordinarily are carried away by the circulation and disposed of. Muscular asthenia may be due to an increased production of these toxins or a reduced capacity to carry them off as manufactured. Both causes are commonly associated, and the latter probably is the more important.

A Toxic Vicious Circle. If the circulation is insufficient, i.e., if the blood pressure is low and the "circulatory pep" is below par or, in other words, if the regulating mechanism which controls circulation, cardiac efficiency and blood pressure, is not efficient, asthenia must result from the accumulation of the ordinary amounts of cellular wastes. This would be aggravated if in addition to this there is an augmented production of these products. It also happens that poor circulation causes poor oxidation, which in turn causes an accumulation of intracellular wastes. So we have a vicious circle, the one condition aggravating the other and vice versa.

The tendency of the cell is to die. "Man begins to die as soon as he is born." This means that if the perpetual production of wastes is modified ever so slightly or the efficiency of the emunctories fails, there is going to be trouble. And the initial manifestation of this kind of trouble is asthenia.

What is the earliest symptom of incipient tuberculosis? Asthenia. What is the chief sign of the other most common toxemia—intestinal stasis and alimentary intoxication? Asthenia. What is the commonest factor in any infection, focal or otherwise, or infectious disease? Asthenia.

What underlies the asthenic syndrome? We have already said that toxemia, intracellular or extracellular, is the commonest cause, but how does it bring it about? In the answer to this question lies the basis of a new conception of disease, and a new, or at least an ignored, method of treatment. *The chief cause of asthenia is insufficiency of the adrenal glands.* Hypoadrenia is probably the most common endocrine dysfunction. It deserves consideration wherever there is asthenia, no matter whether it is called neurasthenia, psychasthenia, myasthenia or any of the numerous other names given to various clinical manifestations of the one fundamental underlying trouble.

"Why do you connect the adrenal glands with the asthenias?" This question has been put to me a hundred times or more. Here is the answer as concisely as I can give it: The adrenal glands produce an internal secretion which is known to exert an amazing influence upon the circulation. Adrenin, as this hormone is called, is a predominant factor in the maintenance of cellular tone and especially that of the unstriped muscles of the heart and intestines, it keeps the blood pressure up, it thus favors both oxidation and detoxication (and it has been shown that adrenin also has a direct influence upon oxidation besides its indirect effect through its control of circulatory efficiency); by its musculo-tonic effect, digestion and alimentary tone is maintained, hence hypoadrenia favors a condition of atonicity of the alimentary musculature which, in turn, causes stasis and further toxemia,—another of the dread vicious circles. This hormone, adrenin, has been shown to "control the sympathetic system,"

thereby bringing about the conditions just mentioned as well as other subtle chemical regulations which need not be mentioned in this brief article.

The Sensitiveness of the Adrenal Glands. Poisons of any kind, in the most minute dosage, have an immediate effect on these most sensitive of all the organs of the body. It is the business of the adrenals to respond to these influences, for if they do not do this, the increased circulation and augmented oxidation, which become essential and which are brought about automatically as the body's greatest means of protection against disease, fail to take care of the toxemia. It is true that there are innumerable forms of toxemia, some toxins which are the usual wastes of the body cells, some which are unusual as the products of intestinal putrefaction, some which we ingest wilfully (as coffee) or accidentally, some which are produced by the aberrant activity of certain organs and especially the endocrine glands (for "too much of a good thing is a bad thing"), and, finally, some poisons which are automatically made in the subtle chemical changes which occur in shock, emotional storm or the various mental states like fear, rage, worry and so forth. In other words, practically all forms of stimuli of the nature mentioned stimulate the adrenals. Too often the persistence of these stimuli is more than these little glands can bear, and they play out. We have as a result a functional hypoadrenia, *and the first symptom is asthenia plus.*

It should be unnecessary to give clinical proof; it is so extremely common. We have already mentioned the asthenia of the earliest stages of tuberculosis, before the cough and sputum materialize. We know that "post-influenzal asthenia" is indeed a most uniform result of the toxemia of this scourge. We know that following pneumonia, typhoid, malaria or any acute infectious disease, hypoadrenia is the rule. We know that an emotional shock—bad news, an accident, an unusual and strenuous mental impression as seeing an accident or death—will cause a "let-down" that is nothing but a more or less serious manifestation of adrenal asthenia. In some unusually susceptible individuals—those for instance, whose adrenals have had much to put up with—far less important stimuli, as an unexpected noise or a slight "tiff" at home, cause an asthenia that is as well defined as it is usual.

From a clinical standpoint, it is impossible to have a combination of conditions such as the various asthenias already mentioned without *endocrinasthenia*—the natural result of functional insufficiency of the glands of internal secretion, or hypocrinism. The adrenals are too intimate with the other endocrine glands to be affected alone. In fact, not only is this endocrinasthenia a very real clinical entity, but it is the underlying cause of the other asthenias, for it is impossible for an individual to be "all run

down" and to be suffering from asthenia without both the cause and the effect exerting its influence upon the sensitive endocrine organs. In other words, when the body is tired the endocrine glands are also tired. When the circulation is slowed the endocrine glands are affected with the rest of the body, and when the vital service of hormone production by the endocrine system is reduced ever so little, we have asthenia as one of the immediate results, whether the toxemia is a prominent factor or not, and the greater this endocrinasthenia the worse do the other forms of asthenia become. We have another serious vicious circle.

The big thing about functional hypoadrenia is the possibility of modifying its effects by supporting the endocrine glands. Thousands of run-down, tired-out, asthenic individuals—many of them labeled "neurasthenia," many called "convalescents," many in whom the asthenia is ignored because it is submerged by some more obvious condition, as rheumatism, ovarian dysfunction, a focal infection or some mechanical difficulty in the abdomen—have as their most prominent and their most responsive symptom asthenia, resulting from a plain case of adrenal insufficiency.

The Symptoms of Adrenal Insufficiency. What are the usual symptoms besides asthenia? Low blood pressure; a subnormal temperature; poor elimination of wastes, especially the urea and other urinary solids (all of which factors are measurable, it should be remembered) and, naturally, malnutrition; loss of weight; anemia and so on. In fact the Addisonian syndrome which results from severe organic adrenal disease is merely an incurable, aggravated form of the very same trouble, the difference being merely one of degree. Does this fit in with several cases on your list now? Yes, indeed. Then why not support the adrenals, in addition to prescribing elimination, rest and other measures to remove underlying causative elements? Adrenal support is a great advance in every-day practice. It works; and the results are sometimes wonderful. It may be given practical application with the greatest facility by prescribing *Caps. Adreno-Spermin Co.*, a pluriglandular formula which I devised, which combines adrenal support from a suitable dose of adrenal substance plus "the dynamogenic hormone" spermin (from the interstitial cells of Leydig in the testes) phosphorus in the form of calcium glycerophosphate and brain substance and a small dose of thyroid.

The obvious and rational measures for the treatment of all forms of asthenia are (a) rest, (b) the removal of as many as possible of the aggravating factors such as toxins, both those produced in the body (alimentary) and those taken into the body, wittingly or unwittingly; and circumstances calculated to stimulate emotional elements, like worry, fear, pain, etc., (c) the natural stimulation of the dynamogenic factors in the body, e.g.,

the glands of internal secretion, by means of organotherapy (on the well-known principle of homostimulation represented in the Adreno-Spermin formula just referred to) and (d) finally, suitable nutrition, both as regards food, water, and especially the mineral elements of the organism. All of these physiological measures should be recommended simultaneously; and many hundreds of experiences with this procedure, more especially when "adrenal support" is given as suggested, convince one that this endocrine encouragement "increases the pep" or, in other words, antagonizes asthenia. In this connection, it may be remarked that in addition to bringing about a noticeable change in the tendency to muscular fatigability or tiredness, it is possible to get a very fair idea of the benefit *in figures,* for such treatment increases the lowered systolic blood pressure, increases the subnormal temperature and increases the elimination of urinary wastes, especially urea.

The Essentials of Adrenal Support. The matter of giving consideration to the adrenal or endocrine factor in asthenia is important in the extreme, and if organotherapy is rational in Addison's disease it is doubly so in these functional conditions since they are far more likely to respond to this physiological support. For convenience some of the essential facts are arranged below in semi-tabular form so that they may be the more readily appreciated and applied:

Physiology. The Adrenal Hormone (adrenin)

(1) Regulates the sympathetic system;
(2) Maintains muscular tone;
(3) Supports cardiac action;
(4) Keeps the blood pressure up;
(5) Facilitates oxidation and
(6) Antagonizes fatigue.

Adrenal Function is deranged by

(1) Toxemia (acute and chronic)
Food poisons and drugs; intestinal stasis; focal infections; infectious diseases.
(2) Emotional Stimuli
Fear and worry; pain; shock.
(3) Dyshormonism
Such as ovarian disease, thyroidism, etc.

The adrenals co-operate with the other endocrine glands, especially the thyroid and gonads.

Diagnosis. Adrenal Depletion (hypoadrenia) may be diagnosed by noting two or more of the following:

1. Asthenia, "the fatigue syndrome," with muscular and psychic inefficiency or "lack of pep;"

2. Hypotension with cardiasthenia, cold extremities and internal venous stasis—the so-called "hyposphyxia" or of Martinet;
3. Hypothermia—subnormal temperature;
4. Malnutrition due to the poor oxidation and elimination;
5. Acidosis in greater or less degree is also naturally present.

Therapeutics. Adrenal support by suitable organotherapy properly should accompany detoxicative and hygienic measures.

Adrenal Substance homostimulates the adrenals and replaces, in part, the deficient adrenin.

Spermin from the Leydig cells of the gonads stimulates muscular tone (dynamoganic) and cell chemistry.

Lecithin is "the most easily assimilated phosphorus."

Thyroid Extract encourages endocrine action generally, and in hypoadrenia there is always hypothyroidism.

Calcium Glycophosphate is not only a useful mineral but is considered to have an especially beneficial effect in neurasthenic conditions.

The above are suitably combined in an effective pluriglandular formula, *Caps. Adreno-Spermin Co.*, which supports the adrenals, antagonizes asthenia and raises lowered blood pressure.

SECTION V. CHAPTER 2

ADRENAL SUPPORT IN TUBERCULOSIS

In a recent issue of *The Organotherapeutic Review* a correspondent, the Superintendent of a sanatorium in Indiana, wrote the query department as follows: "I would be very pleased to receive your suggestions for the use of organotherapy in tuberculosis. The asthma, the low blood pressure, the chronic continuous poisoning, the low Arneth blood count surely indicate a condition needing special boosting and more than we have been in the habit of giving."

The syndrome mentioned by this writer is, to my mind, essentially of endocrine origin. Practically every one of the symptoms enumerated are related to disturbed adrenal function; and I believe that the adrenal element in the tuberculous is as early, constant and important as any other factor, whether cause or effect. Perhaps the truth of this statement can be verified best by testing in "the crucible of the clinic." Clinical results are the only factors that count for very much in medicine. We can theorize all day, but this does not cure our patient. It may be all right to theorize; but it is far more practical and helpful to establish

the reasonableness of some suggestion that may be new to us than to pass it up without thought.

A great many items have been published, especially in French, on the advantages of various organotherapeutic procedures in tuberculosis. Some of them are sound; some are questionable. We still have the tuberculosis, and all these statements have not controlled this plague. I am not pessimistic, however, for some of these reports are really "getting us somewhere," especially the splendid contributions of Dr. Emile Sergent, of Paris, whose original interest in *"l'insuffisance surrènale"*—hypoadrenia—centered in his studies of the tuberculous, and from which has been developed much of real value in endocrinology. Sergent is an accepted authority; he has proved his points. His "Collected Papers on Adrenal Disorders—1898-1914" is a wonderful book, though it is in French, of course. Suffice it to say that Sergent has shown us that adrenal insufficiency is *the rule in tuberculosis.* In fact, the first suspicious manifestations of tuberculosis are of adrenal origin, for asthenia or "the tiredness of incipient phthisis" is the essential initial symptom, to be followed shortly by the subnormal morning temperature,—and all this before there may be any cough or sputum.

Adrenal Insufficiency Predisposes to Tuberculosis. It cannot be denied that every person with tuberculosis, whether of the lungs or elsewhere, irrespective of the stage of the infection, has a pair of unduly burdened adrenal glands which are expected to regulate many vital sympathetic functions and which are subject to the baneful influence of those very disorders of metabolism which predispose to the infection. Poor oxidation, malelimination, bad nutrition, affect the adrenals before the invasion of the bacilli. The adrenal factor discussed in the previous chapter almost invariably antedates the actual infective process. Did you ever think how common a predisposing cause to tuberculosis is a cold, la grippe or the "flu?" Have you found out that hypoadrenia is quite the biggest factor in influenza, pneumonia or even a bad cold? That it is due to the bacterial and other toxemia and is the reason for the uniformly low arterial tension, the severe asthenia and the invariable hyposphyxia? And, by the way, this circulatory syndrome described by Prof. Alfred Martinet is extremely common in tuberculosis. "Hyposphyxia" is a condition of poor circulation, with cold extremities, internal venous stasis (abdominal and pulmonary), cardiac weakness and *hypotension.* These individuals are suffering from hypoadrenia; the adrenals are supposed to maintain circulatory and cardiac tone, and being depleted the circulatory cause of tuberculosis obtains.

Why should not adrenal support be rational in tuberculosis as it has been proved time and again in influenza? It is, and the raised blood pressure is not the only obvious benefit, either. There is a production of "pep" quite similar to that we have

found from strychnia or other time-worn tonics, but it just happens that this fatigue-antagonism is not due to stimulation but to a more nearly normal physiology (on the part of the adrenal system) resulting from the homostimulation (see Section II, Chapter 2), which means better circulation, better oxidation and a diminution of causes rather than effects. Is not this logcal?

The Toxic Element in Tuberculosis. Again consider the matter from another standpiont. It is certain that every sufferer from tuberculosis is toxic; not merely from focal poisoning, but from alimentary intoxication. The toxemia antedates the infection; and when the infection has become obvious the toxemia is so much the greater. Toxemia is the greatest single cause of adrenal stimulation. It must be thus, for it is a large part of the functions of these little glands to react to the slightest poisoning —irrespective of its origin—so that the circulatory and detoxicating mechanism which they control may be stimulated in order to control the toxemia and its effects. Overstimulation produces hyperadrenia, the most usual findings of which are sympathetic irritability, dry mouth and throat, and the occasional "digestive crises" which come on without apparent cause and pass off very soon. It should be stated here that a condition of well-defined hyperadrenia is rare, merely because the adrenal principle—adrenin—is oxidized with unusual ease and rapidity (that is why adrenalin-therapy is less efficacious in prolonged hypoadrenias) and, too, because the adrenals cannot stand prolonged overstimulation, and become depleted—knocked out!

So adrenal insufficiency is indeed common in tuberculosis. In my estimation there never was a case in which the adrenals were not involved, though I do not want it understood that I am referring to actual cellular pathology or adrenal tuberculosis. I repeat: *Tuberculosis is a disease in which the adrenal functions are seriously impaired.* The chronic continuous poisoning referred to by this correspondent is exerting its inexorable influence upon the adrenals with the result that muscular fatigue is the rule, oxidation is below par (study the urinary solids and be surprised at the uniformly poor elimination), the temperature is subnormal at times, the blood pressure is 110 or less—very ordinarily less, depending upon the length of time that the adrenals have had to stand the toxemic hammering—and the patient is "all run down." The syndrome of hypoadrenia is complete. We have a "functional Addison's disease," which may and occasionally does develop into the real Addisonian syndrome, which consists of the aforementioned symptoms in an aggravated degree, as well as the typical pigmentation and Sergent's "white adrenal line."

The Rationale of Adrenal Support. Now if this sounds sensible, why should we not in addition to our other efforts in the line of hygiene or medication attempt to support the overworked

adrenals? Candidly, I do not believe that adrenal support will make any direct and material difference to the extent of the infection, nor that it will reduce the virulence of the invading organisms, whether the *B. tuberculosis* or the invariably associated pyogenic cocci. But I most assuredly believe in adrenal support, whether as a part of the treatment of tuberculosis or any other condition in which the adrenals are depleted. If some of my colleagues would only get the idea that I do not believe in organotherapy as the treatment of this, that, or any other disease, and that the study of endocrine function is or should be *a part* of the complete study of a given case, they would be less liable to mislead themselves—and others.

Is tuberculin a good thing? Most of us will say "Yes." Shall we ignore it, then? No; we will judiciously add it to other indicated measures. Why not the same attitude to the important subject under discussion? One remedy or procedure may be ever so good, but it does not necessarily follow that it is, therefore, *the* treatment. We will continue to use suitable diet and hygiene, tuberculin may help a lot, so will proper intestinal antisepsis (I am convinced that benefit from guaiacol, Thiocol, Calcreose or other similar remedies is more decidedly alimentary than pulmonary) and to all this add a careful consideration of the adrenal functions. If they are really depleted and the patient shows the usual syndrome already mentioned, let us encourage adrenal physiology by homostimulative organotherapy in the same way we have been doing this for years in other conditions of hypoadrenia. This fits in splendidly with our other measures in the treatment of tuberculosis *and supplements it*, let me emphasize, not supplants it!

I have hesitated to say very much in my literature about my formula No. 1, *Caps. Adreno-Spermin Co.* in tuberculosis, because I felt that I would be promptly misunderstood and branded as attempting to capitalize the attitude common to the tuberculous and to many of their medical advisers and be criticised for boosting this formula as a remedy for this particular disease. It is not; but it tends to raise a lowered blood pressure—by actual sphygmomanometry, it increases oxidation—by the urinary findings, it certainly favors the cellular chemistry, and hence nutrition, and does so by supporting the adrenals. And if the adrenals are depleted, no matter whether the name of the accompanying disease is Addison's disease, neurasthenia, post-influenzal asthenia, tuberculosis or what-not, to support them and favor the betterment of their all-important functions is a sound therapeutic procedure.

Possible By-Effects. A point has come up a number of times in regard to possible by-effects of this method. For instance, one physician inquires: "Do you feel that it is safe to give the *Caps. Adreno-Spermin Co.* to a patient with advanced

tuberculosis who has previously had hemorrhages but whose pulmonary condition has been quiescent for a year, the blood pressure being within the normal limits? Would you expect this preparation to give relief from the neuro-muscular asthenia in this case? Do you consider that tuberculosis *per se* is a contraindication to any one of the glandular products?"

The Adreno-Spermin formula is active for three reasons: It supports adrenal function and thereby raises sympathetic tone, including abnormally low blood pressure, etc. It has a dynamic effect, especially on muscle, due to both the adrenal content and the spermin, which is believed to be the best musculo-tonic remedy of its kind. It contains neuro-tonic elements (lecithin and a generous dose of glycerophosphate of calcium) and hence has some effect upon nutrition, especially where phosphorus is likely to be helpful.

I do not believe that the adrenal stimulation brought about by the small and gradually active doses of adrenal substance would favor hemorrhage in a case such as is mentioned, though pituitrin or adrenalin injections might be contraindicated for their decided and temporary pressor influence. The Adreno-Spermin formula has no immediate or active effect—it is very gradual in its action and therefore less likely to have contraindications. Remember that organotherapy is really a form of endocrine education. The homostimulant effects of gland extracts favor the re-establishment of normal endocrine function in the glands which correspond to those from which the extracts are made. This explains a large part of the benefits obtainable from organotherapy.

Such treatment supports the adrenals and gradually raises an abnormally low tension; but in a normal individual it makes little or no difference to the average blood pressure.

Tuberculosis is not a contraindication against organotherapy. In fact, with the exceptions just mentioned—the rapidly acting pressor principles—organotherapy may help much as has been suggested. Again, if a tuberculous girl has an ovarian dystrophy, to mitigate it by suitable organotherapy surely is proper; just as an individual with hepato-biliary insufficiency who happens to have tuberculosis will benefit from suitable hepato-biliary stimulation as with the use of my *Caps. Hepato-Splenic Co.,* which, by the way, seems to have a good effect on malnutrition with alimentary laziness and has been used with benefit in many cases of tuberculosis in which the digestive element was prominent. (Note that this contains the Adreno-Spermin formula plus other hepatic supporting products—see formula on page 74.)

The subject is a large one, requiring more space than can be given to it here. The great point to remember is this: If adrenal function is depleted *and ignored,* our best therapeutic efforts will be less effective because of the extreme importance to resistance of the circulatory, sympathetic and metabolic functions main-

tained by these glands. The tuberculous individual has a hard enough fight—any assistance that we can render is worth while, especially when it is so necessary, so generally overlooked, and so comparatively easily accomplished by means of a suitable organotherapeutic support *added to the other indicated treatment.*

SECTION V. CHAPTER 3

THE TREATMENT OF OVARIAN DISORDERS

Functional ovarian disorders include developmental, menstrual and climacteric disturbances and represent a very large proportion of all of the diseases of women. We have seen elsewhere ("The Diagnosis of Ovarian Dysfunction," Sec. IV, Chap. 8) that the ovaries are responsible for many factors in the normal development and functioning of the body and that they themselves are intimately associated with other glands of internal secretion, notably the thyroid and pituitary.

As has been explained, there are two chief classes of ovarian dysfunction—insufficient endocrine activity and hypersecretion. Since the ovaries play such an important part in the essential changes known as secondary sex characteristics, any ovarian insufficiency that manifests itself before development is complete will cause more extensive results.

Functional Ovarian Insufficiency. As a result of various causes, nutritional (hormonic), nervous and circulatory, ovarian function may be insufficient. I think this is quite the commonest glandular insufficiency among women unless perhaps we should give first place to the adrenal insufficiency which follows toxemias, acute infectious disease and shock. At all events, hypoovarism is a most usual finding in general practice and the chief results are amenorrhea, dysmenorrhea and the various neuroses resulting from these disturbances. The treatment of ovarian insufficiency with organotherapy is one of the accepted organotherapeutic procedures, and while there is some difference of opinion as to the relative merits of glandular extracts of the corpus luteum or total ovary, there can be no doubt that the principle of homostimulation fully outlined in the second section of this book may be applied with great advantage in the control of conditions of this character.

For fifteen years or more, functional pelvic disorders and the reflex disturbances resulting therefrom have been treated with corpus luteum or ovary alone, and for obvious reasons no method or drug can begin to take the place of such preparations, merely because the same principle applies that does in hypothyroidism—

the body is not making enough of a certain substance and is suffering from the lack of the stimuli made possible by that substance; we intervene by securing a similar substance from animals, administer it to the patient, and the body is able to take it up and use it to re-establish its own affairs. Hence, extracts of this character not merely stimulate the gland which corresponds to that from which it was made but replace, in a degree, the hormone that may be lacking.

Numerous clinical experiences by literally hundreds of physicians now connect the thyroid gland with the ovaries. A number of quotations from a communication by Oliver T. Osborne emphasizing this fact will be found in the other chapter on ovarian disturbances (Sec. IV, Chap. 8) which, by the way, should be read in conjunction with these remarks. Suffice it to say that hypothyroidism and hypoovarism go together clinically and deserve to be treated together organotherapeutically.

When I was in Paris in 1913, I learned that Prof. Paul Dalche, of the Hotel Dieu, was in the habit of routinely adding a centigram a day of thyroid extract to the ovarian treatment of menstrual difficulties, the reason being that sometimes the ovarian difficulty was really of thyroid origin more than of ovarian origin and while direct ovarian stimulation might be good, a consideration of the associated and causative elements at the same time would be much better.

The same principle applies in regard to the pituitary gland. We know that pituitary insufficiency causes ovarian insufficiency; hence, if we have a case of functional hypoovarism, how do we know that there is not underlying it a pituitary insufficiency? And, on the principle which I have outlined in my hypothesis of hormone hunger (see Sec. II, Chap. 5), the body is capable of making the most use out of the things that are given to it in proportion to the respective needs of the various organs which may be involved in the symptom-complex.

Amenorrhea of all shades, as well as dysmenorrhea, and many of the intangible circulatory and nervous disturbances associated with these disturbances are quite the most satisfactorily treated by pluriglandular therapy for the reasons already given. For years I have been using with marked success a formula now called No. 4, *Caps. Thyro-Ovarian Co.*, which contains, in addition to ovarian substance with corpus luteum, a small dose each of desiccated thyroid gland and total pituitary substance. It is warmly recommended as a part of the treatment of the usual functional pelvic derangements of ovarian origin and is believed to excel corpus luteum alone merely because the luteal function is practically never involved alone.

Routine Administration of Caps. Thyro-Ovarian Co. Since the ovarian hormone function is cyclic and varies considerably during the month, one can increase the value of this pluriglandu-

lar formula by arranging the dosage so that it is omitted at certain periods and pushed when likely to have the widest physiological effect. Incidentally, this is quite a convenience to the patient and, at the same time, reduces the expense of the treatment. Prior to the consummation of this monthly task—at the very time when the nervous and circulatory difficulties which accompany amenorrhea are greatest—we can re-enforce the hormone function in proportion to the needs by increasing the dose; hence I have suggested the following cyclic method of administering *Caps. Thyro-Ovarian Co.* which has proved very satisfactory: Instruct the patient to omit the capsules entirely for a period of ten days following the onset of the menstrual flow. This includes the whole menstrual time, which is believed to be just after the time when the ovarian endocrine activity has reached its monthly peak. During the next ten days, i.e., the middle of the month, one capsule is given three times a day, while for ten days or a week, depending upon circumstances, immediately before the next flow the dose may be pushed by doubling the number of capsules. This is again stopped as soon as the flow shows itself; and since there is but a short time during each menstrual month that the ovaries can be stimulated effectually and this organotherapy is a means of re-establishing a normal cellular activity, such treatment should be continued for a number of months, and if the results are good—and very commonly they are splendid—it should be continued for some little time after an apparent cure has been secured.

Menopausal Difficulties. The disconcerting circulatory disturbances connected with the change of life, and enumerated elsewhere, are evidently due to the same sort of a cause as other forms of amenorrhea earlier in life and respond very satisfactorily to the replacement of a part of the necessary quantity of ovarian hormones. In the climacteric especially, the value of pluriglandular therapy should be obvious, for it is well known, for instance, that during the decade between forty and fifty serious forms of hypothyroidism in women are most common and that the menopausal difficulties are by no means entirely of ovarian etiology.

Psychoses and Insanity. Unfortunately, in some remarkable manner the imbalance due to dysovarism may cause more or less serious disturbances of a mental character, and one of the dreaded results of severe ovarian dystrophies is insanity. We prefer to call it "ovarian psychosis" and, irrespective of the complexity of the cause, to attempt its treatment by the regulation of the ovarian difficulty that shows itself simultaneously. In other words, an ovarian psychosis may respond to ovarian therapy just as other less serious nervous conditions; and while the prospects are not so good because the trouble is more serious and comprehensive in its effects, they are better than the other forms

of psychosis. This means that mental disturbances in women that may be connected with ovarian dysfunction may be modified favorably by direct attention to the ovarian disturbance. A number of experiences of this character following the use of my *Caps. Thyro-Ovarian Co.* have been brought to my attention, one case being particularly interesting: I was surprised to receive a letter from San Diego in which the following sentence appeared: "I am getting some wonderful results. One young lady who was diagnosed as suffering with dementia precox, has made a complete recovery. They sent this lady to a sanitarium and paid out about seven hundred dollars with absolutely no apparent benefit. I put her on the Thyro-Ovarian Comp., and sent her up into the mountains. One month did the work. She does not even have a suggestion of her former trouble." I immediately wrote the doctor that I did not believe that the case could have been properly diagnosed and that the condition evidently was an ovarian psychosis and not dementia precox. Eleven months later, I had occasion to visit this physician and learned, to my pleasure, that there had been no recurrence of the mental abberation and that the young lady was in better health than at any time previously.

Organic Ovarian Insufficiency—Infantilism. If for some reason (usually associated with insufficiency of the thyroid or pituitary, or both) the ovaries do not develop and the internal secretory function of the corpora lutea does not materialize at the ordinary time, i. e., at puberty, there will be no menstruation. In addition to this, the growth and development of the essential reproductive organs, including the uterus and ovaries themselves and the external genitalia, as well as the breasts, will be prevented. This condition is known as hypoplasia, status hypoplasticus, or infantilism; and while there are some prospects for its treatment, obviously they are not so good as in less serious disturbances that show themselves later.

The treatment of infantilism is not an encouraging proposition. It should involve a study of the possible causes in other ductless glands, including a test of thyroid function (see Sec. IV, Chap 4), a study of the pituitary gland, both from the standpoint of the radiographic examination of the sella turcia and the measurement of sugar tolerance, etc., and search should be made with the fluoroscope for a persistent thymus. All of this, in addition to the careful study of the whole body, as well as a pelvic examination if this is at all feasible. It is necessary to strip the patient because infantilism does not necessarily involve developmental difficulties—it is quite a different proposition from cretinism, although infantilism is one of the symptoms of cretinism—while it does cause definite changes in the form and distribution of hair. If the usual pads of fat on the hips and, generally speaking, the feminine contour as seen from behind is absent, and the axillary and pubic hair is considerably lessened or entirely absent

and mammary development does not appear, or is defective, in all probability we have a case of true infantilism. There are only two things to do in cases of this character: first, to remove any obvious causes of the trouble as, for example, malnutrition or a persistent thymus; and second, to homostimulate not merely the ovaries which may be present in a rudimentary form, but also the glands which control ovarian function and in which a disturbed internal secretory activity may be taking place which may be the underlying cause of the difficulty. Hypopituitarism and the more serious forms of hypothyroidism both may bring this about, and the only treatment worth considering is endocrine treatment. Such organotherapy should consist of the persistent administration of pluriglandular formulas including the thyroid, pituitary and ovary (i. e., either No. 4, *Caps. Thyro-Ovarian Co.,* or S. F. No. 73, *Caps. Gonad-Ovarian Co.,*—a similar preparation to No. 4, to which a generous dose of anterior pituitary substance has been added). The dosage usually is three or four of such capsules a day, and it must be continued for a long period and may be supplemented by other circulatory stimulating measures like hydrotherapy and osteopathy. In fact, I know of several cases of infantilism that seem to have been very materially benefited by the neuro-circulatory changes which have resulted from intelligent spinal manipulation.

Sterility and Sexual Apathy. While these two conditions need not necessarily be associated with one another, they may be given brief consideration together. Provided organic elements in the former and psychic elements in the latter can be ruled out, it is very probable that the whole trouble is of an endocrine nature. At the close of an interesting paper by Novak (*Jour. A. M. A.*, Aug. 5, 1918), this writer makes the following pertinent statement: "The reason for the failure of this method of attacking the problem (dilatation or local interference) lies in the fact that the sterility is most likely due to a physiologic defect in the endometrium, that is, the absence of some factor essential to the implantation of the ovum. Here again we hark back to disorders of the internal secretory system as the ultimate cause. This, after all, is the conviction borne in on anyone who studies this general problem, whether or not he be a ductless gland enthusiast or 'faddist'—the conviction that the day will come when these very numerous cases of primary amenorrhea, primary dysmenorrhea and sterility, which are associated with uterine hypoplasia, will be successfully treated by correcting the endocrinopathy responsible for the uterine defect."

The following letter received from a prominent gynecologist is interesting in this connection: "I was very much interested to have one of my old patients report a few days ago that she was 4½ months pregnant. She originally consulted me last spring for sterility, having been married two years. I first had

her on lutein for a number of months with no result. She is a strong, healthy woman in every way and there was no apparent reason why she should not conceive. Shortly before my departure for France in July, I put her on your Thyro-Ovarian Compound with the happy result that she became pregnant in September and is now under my care for confinement. I am quite sure that the gland stimulus she received was the important factor in bringing about the desired condition."

Sexual apathy or lack of libido may be a purely endocrine proposition and deserves consideration and treatment from this standpoint. We know, for instance, that in myxedema (hypothyroidism), Froehlich's dystrophia adiposogenitalis (hypopituitarism) this reaction is lost, and also that it may be lessened almost entirely by ovarian insufficiency; hence, a treatment embodying these three principles, added to advice in regard to fundamentals, is likely to be efficacious and indeed has been many times, and the use of preparations of the character under discussion here offers better possibilities of success than any other measure that I know of.

The Treatment of Ovarian Irritability. The treatment of hyperovarism naturally is the opposite of the measures just discussed and involves the principle of hormone antagonism exerted by the mammary glands upon ovarian function. This subject is taken up quite fully in the chapter devoted to this subject (see Sec. V, Chap. 14, "Mammary Extract in Therapeutics").

Ovarian Poisoning. Still one more feature of dysovarism must be mentioned: As we have learned, there is a condition which has been called ovarian poisoning which results from a perversion of the function of the ovarian cells, usually associated with structural changes such as the development of tumors, etc. This dysovarism is far more serious than any of the functional conditions mentioned previously; and while the ultimate successful treatment calls for the surgical removal of the abnormal tissue, it may be that there is a serious adrenal depletion as a result of the toxemia as well as the series of difficulties which are due to ovarian insufficiency. In other words, in those cases where the manifestations of ovarian hypofunction are marked and they are associated with the syndrome of adrenal insufficiency, which includes marked fatigability, low blood pressure and generally reduced cell chemistry, it may be advisable to combine adrenal support with the organotherapeutic regulation of the ovarian difficulty, and for cases of this character a special formula, No. 79, *Caps. Adreno-Ovarian Co.*, may be advisable. The dose and method of administration is quite similar to the thyro-ovarian preparation already discussed.

Parenthetically it may be stated here that it has been decided to add some suitable coloring to this S. F. No. 79 so that if it ever seems to be necessary to "change the medicine" for

psychic reasons, as in the treatment of a neurasthenic young woman, the *same* treatment can be continued, though *it looks different!*

SECTION V. CHAPTER 4

GALACTAGOGUE ORGANOTHERAPY

The appreciation of the factors responsible for the establishing and maintenance of satisfactory lactation is obviously of fundamental importance to human welfare and of much practical value in general practice.

Deficient milk production—agalactia or hypogalactia—is common enough, and aside from the influence it may have upon infant health and mortality, it also has a very definite physiological relation to pelvic disturbances in the mother, for nursing is a normal factor in ovaro-uterine physiology, and those who will not or cannot nurse their children often have to suffer for it later on.

There are no very well known galactagogue remedies. The administration of plenty of milk and cream and other dietetic care usually constitutes the best that we can do. We feed cotton-seed cakes to our cattle because gossypiin is a recognized galactagogue, yet this principle is rarely used in medicine. Various malt preparations and special foods are recommended, all of which act indirectly.

Hormone Control of the Mammæ. Mammary development and secretion seems to be so definitely under the control of hormone influences—the ovarian hormone stimulates mammary development, a hormone produced in the fetus itself causes the formation of milk, the placenta also has something tangible to do with this, and finally the absence or removal of these various factors causes a stoppage of this function—that it seems that it should be possible artificially to bring about desired stimulation by some form of organotherapy. With the well established principle of hormone stimulation in mind, it was natural to try the administration of mammary substance, and some indubitable results have followed this procedure. It seems established that mammary extract is a galactagogue. Some experimental work upon cows, at Cornell University, has also demonstrated that the pituitary gland contains within it an active galactagogue principle, and a number of records in the literature of agriculture as well as medicine indicate that its use for this purpose is at least feasible.

Further, and most important, the placenta has been found not

merely to be an organ of internal secretion but to be a means of artificially increasing a deficient supply of milk. It is interesting to know that quite recently a French scientist, de Kervily, has shown that certain vacuolated cells normally found in the placenta are actually secretory elements and presumably similar to the internal secretory cells of the pancreas, which are found in the islets of Langerhans.

Placenta Substance as a Galactagogue. The original use of this measure seems to be very old, and unquestionably, is based upon the observation that domestic animals, almost without exception, manifest a remarkable and uniform instinct to devour the placenta as soon as it is delivered. It is clear that these ainmals do not eat the placenta through hunger or instinct to keep the nest clean, for it will be recalled that the cow is herbivorous and has no nest!

Some very practical and interesting experiences were obtained by Dr. Bertha Van Hoosen, of Chicago, who made a number of experiments at the Mary Thompson Hospital (*Woman's Med. Jour.*, Dec., 1916). Thirty grains of desiccated placenta were given daily to a series of cases in six doses an hour apart. The first report was a complaint from the nurses—the patients had so much milk that it was a burden to keep the breasts empty! A case is mentioned in which 16 ounces of milk were removed after the infant had taken all it would. Three others had 6 ounces removed immediately after nursing. A fifth patient had 8 ounces, and a sixth had 4 ounces removed under like circumstances. Generous quantities of superfluous milk were obtained without depriving the child, the only object being to secure comfort for the mother. Tabulated findings indicate that the infants of placanta-fed mothers maintained or increased their birth weight at the end of the second week, whereas comparisons between a large number of treated and untreated indicated that the average loss during the first week was 9½ ounces, whereas in the cases where desiccated placenta was used the average loss was only 5½ ounces for the first week. During the second week, the average gain was 50% greater than in the untreated infants, the conclusion being that the "administration of desiccated placenta produces an early and gradual stimulation of the secretion of milk and no other by-effects."

R. T. Frank, of New York (*Jour. Cancer Research*, 2, 1917), determined that placental extracts "experimentally stimulate the breasts, increasing the area and developing the ducts, acini and nipples." S. W. Bandler, also of New York, includes mammary extract and placental substance among "the valuable opotherapeutic products." (*Endocrinology*, June, 1919.) E. L. Cornell, of Chicago, reports some experiences with the galactagogue influence, especially the indirect effect upon the infants. Of the cases studied, 87% began to gain on the 4th or 5th days, as

against 69% of those whose mothers did not take the extract. Of the treated cases, 44% regained the birth weight before leaving the hospital, as against only 24% of the latter. Very little attention has been paid to statistical studies of this character, and these figures are an additional encouragement to those who have been urging this matter for years.

Many experiences have amplified these opinions, and it has also been discovered that the post-partum conditions in the pelvis are favored by this treatment. In other words, uterine involution is more satisfactory following placental feeding.

Much experimental work has been done, and it has been found that preparations of this character not only exert a tonic involuting influence on the post-partum uterus, but according to Ercole Cova, an Italian investigator (*Annal. Ostet. e Gin,* Sept., 1915), placenta extracts may be used therapeutically in the treatment of hypoplastic uterus, for it seems that there is a principle in the placenta that causes growth of the uterus, both during pregnancy and in abnormal infantile cases. This particular phase of organotherapy has not been given much consideration as yet, but it seems quite promising.

A Pluriglandular Galactagogue Formula. For a number of years, I have been recommending a formula embodying the three glandular preparations mentioned here—mammary substance for its hormone stimulant effect upon the mammary glands, placenta for its indubitable galactagogue effect, and pituitary gland for its possible benefit to milk production and its associated value as a general and uterine tonic. This formula, under the name No. 3, *Caps. Placento-Mammary Co.*, has been used for some time with quite unusual success when there has been a serious reduction of the amount of milk secreted; but it is more rational as a prophylactic and is recommended as a routine procedure following labor. The initial dose is two capsules at each of three meals daily for ten days or two weeks, thereafter continuing the administration of one capsule three times a day for several weeks.

There also seems to be some relation between nursing, the administration of placental extract, and early menstruation after pregnancy. I recall a recent inquiry from a colleague, who asked if the *Caps. Placento-Mammary Co.* prevented menstruation. I was noncommittal in my reply, because I really did not know. I said that it was supposed to favor the establishment of normal post-partum conditions, including the milk supply and uterine involution. I remarked that menstruation during lactation was not normal, and was not surprised to learn the following case report: A 3-para who had had difficulty in nursing her other children, and who has always menstruated five or six weeks after delivery and thereafter fairly regularly, had been given the *Caps. Placento-Mammary Co.* to obviate the expected diffi-

culty with the nursing, if that were possible. The response was splendid and there was enough milk and to spare, but to the surprise of the patient she did not menstruate for over five months, during all of which period she was satisfactorily nursing her baby.

Many reports indicate that this is an effective galactagogue, and I believe that its influence is altogether along natural lines; therefore, it is eminently rational.

SECTION V. CHAPTER 5

INTESTINAL STASIS AND THE INTERNAL SECRETIONS

Sir Arbuthnot Lane, of London, who has prominently brought forward certain phases of the subject of intestinal stasis, repeatedly has called attention to the frequent endocrine manifestations associated with this common syndrome. These are naturally the result of the absorption of poisons and this toxemia in turn, is responsible for further endocrine dysfunction which causes certain symptoms and, at the same time, aggravates the disturbed cellular chemistry thereby making a vicious circle.

It is well known that moderate forms of hypothyroidism, for instance the socalled *"myxedeme fruste,"* cause a serious cellular infiltration which affects the whole alimentary tract with the rest of the body, thus favoring an atonic and functionally inactive state which speedily becomes a mechanical as well as secretory condition. Attention has been frequently called to the baneful effect of the chronic toxemia of intestinal stasis upon the endocrine organs and especially the adrenal glands.

With this brief introduction in mind relaxed abdominal walls, visceral ptosis and intestinal stasis must not be considered as purely abdominal lesions of anatomical interest. Mineral oil may be well enough as a remedy; but it does not get far beyond the intraintestinal conditions. Surgery may be well enough, too, but it does not reach much further than the local, anatomical trouble.

The Endocrine Aspect. There is a side to the study of the symptomatology of enteroptosis that should be worthy of attention equally with the strictly anatomical disorder—the undoubted effects of the associated chronic toxemia upon the glands of internal secretion.

There never was a case of chronic intestinal stasis, or Lane's disease, whose hormone production was at par. Pluriglandular insufficiency or hypocrinism is an inevitable concomitant of any prolonged toxemia of whatever description or origin, just as

toxemia is inevitable with intestinal stasis. So in order to do justice to this large class we must also consider the endocrine side of these cases and in so doing we will assuredly uncover additional possibilities for effective treatment.

Recently Dr. V. Pauchet, of Paris, has given this subject some study and in a recent issue of *La Presse Medicale* (April 11, 1918, p. 189) he has demonstrated very clearly that gastro-entero-coloptosis causes a complex pathologic condition including insufficiency of the glands of the abdomen (liver, adrenals, etc.), degeneration of tissue and an unstable sympathetic nervous system. This refers principally to functions which are under the control of the adrenal hormones and accounts for many of the sympathetic manifestations which accompany and are an indirect result of this ptosis. According to Pauchet persons with ptosis need to be treated for months or years to correct these endocrine disturbances and he recommends hepatic and adrenal organotherapy as well as a general hygienic regime including physical culture, exercise and massage with an outdoor life, psychic re-education, etc.

Pauchet then outlines his surgical measures, which do not interest us for the moment; but I will take the opportunity to direct attention to the organotherapeutic phase of this subject and will emphasize its possibilities as an adjuvant measure in the treatment of intestinal stasis. Parenthetically let me say this: Organotherapy often is of service in conjunction with other indicated measures and very rarely is useful alone. In fact, this is really a rule, for in most instances where organotherapeutic extracts or combinations are indicated practically always they may indicate.

So when the toxemia has reduced the effectiveness of the glands of internal secretion and the ptosis is accompanied by such common symptoms as easy fatigue, severe asthenia, subnormal temperatures, especially in the mornings, malnutrition and the socalled "neuro-circulatory asthenia" (with cardiac asthenia, hypotension and cold extremities, etc.), surely one is justified in attempting to augment the endocrine deficiency by suitable gland feeding.

It is generally admitted that the toxemia of intestinal stasis has a greater influence for evil than the mechanical or anatomic factors. It must be controlled by intestinal antisepsis, diet and other indicated treatment. Organotherapy will not accomplish this. Incidentally, among some printed instruction slips which I use in my consultation work, are two which I will reprint here, as they are often quite helpful in this particular connection:

Intestinal Flushing. The lower bowel is often a source of much toxemia and its proper care may greatly help other treatment which may be needed. The high enema, consisting of a quart of lukewarm water in which a teaspoonful of common

salt has been dissolved, is an excellent preliminary treatment.

This may be introduced into the colon from a fountain- or bulb-syringe and should be allowed to pass in very slowly and be retained for at least fifteen minutes by the clock, preferably while lying down. During this time it is best first to lie on the back with the hips raised and later on the right side and to manipulate the abdomen gently, commencing at the lower left side, running up to the ribs and down on the lower right side. Often this procedure merely loosens the easily removed feces and an oil enema is advisable, for the oil gets into the kinks and crevices. This is given with a bulb syringe preferably following the cleansing enema referred to above.

Secure one pint of any vegetable oil—olive, almond or cotton-seed. Place the bottle in warm water until the oil is at body heat, divide the bottle into thirds by marks on the outside, then place one end of the bulb enema outfit into the oil, squeeze the bulb to empty the air, insert the nozzle and slowly inject about one-third of the oil into the rectum. The previously mentioned positions should be taken and the oil held in all night (sometimes it is necessary to use a cloth to protect the clothing). Repeat this procedure on the two following nights, noting the amount and character of the stools passed the next days.

In cases of severe intestinal irritation it is an advantage to replace one ounce of the pint of oil by one ounce of isarol (or icthyonat), as this has an antiseptic and soothing influence.

Light Exercises for Strengthening the Abdomen. 1. Lie flat on the back (with bladder empty) with knees bent. Gently stroke the abdomen downward, 6 times, along the inside of the left hip, from ribs to pelvis.

2. Stroke 3 times across the abdomen on the navel line from the top of right hip to top of the left, then downward as in (1).

3. Draw the lower abdomen forcibly inward by muscle contraction (not by breathing), and imitate the movement involuntarily made in taking a long, restful yawn—breathe in slowly all the air possible, stretching the trunk and neck forward, then as slowly breathe out all the air taken in, relaxing the body fully. Repeat 6 or 8 times. (This exercise also may be taken sitting or standing and may be repeated often with advantage.)

4. Forcibly draw in the lower abdominal wall (by muscle contraction), then raise it and hold long enough to count ten. Do this 3 times. Rest and repeat.

5. Repeat the series after accustomed to the exercise, but do not tire yourself. Do not apply pressure below and to the inside of the right hip (region of the appendix).

These exercises should be taken on retiring, to overcome the sagging of abdominal organs due to the standing and sitting posture. They may be repeated half an hour or more before meals, if indigestion and gas are present.

These simple instructions have proved quite helpful and despite their elementary character I find that when they are faithfully put into practice it makes a great difference in the routine treatment.

The Thyroid Function Test is Helpful. As has been stated hypothyroidism is a common concomitant of intestinal stasis. It may be the essential cause of the whole trouble. On the other hand it may be a result of the associated toxemia. No matter whether the thyroid element is causative or resultant, it is well to look into the thyroid aspect of these cases, and especially those whose appearance is sallow, whose circulation is sluggish and who may also be suffering from various dermatoses. Under such circumstances it is helpful to use my Thyroid Function Test, by means of which a fairly accurate estimate may be made of the secretory apathy or sensitiveness of the gland. This is explained elsewhere in this book. (Section IV, Chapter 4.) When the chart shows a lazy thyroid, surely the best treatment for the stasis would be incomplete without attention to this factor which, by the way, is commonly ignored altogether.

The Frequency of Asthenia. The most common symptom of intestinal stasis is asthenia. The fatigue syndrome may overshadow all the other symptoms. These patients are tired when they get up in the morning, tired all day and more tired when they go to bed; and the toxemia and other conditions accompanying the tiredness many times has caused such a change in the blood that instead of carrying off the wastes from the brain it is actually irritating to the brain cells and insomnia results. It is, in fact, probably the most common single finding in intestinal stasis.

As I have emphasized in the first chapter of this section, asthenia is the chief indicator of the presence of adrenal insufficiency; and it happens that adrenal insufficiency is a much more usual result of intestinal stasis than dysfunction in any of the other endocrine glands, though the trouble is so thorough in its bad work that the patient with stasis may have any kind of an endocrine disturbance, including the adrenal and thyroid difficulties already mentioned, and pituitary, hepatic and, especially, ovarian disorders.

If every patient with intestinal stasis is likely to have a more or less serious hypoadrenia, pains should be taken to estimate the blood pressure, study the temperature curve especially in the morning for a few days, and learn the amount of urinary solids, particularly urea. It will be found that practically 90% of these individuals have low systolic pressure, subnormal temperature and a markedly decreased elimination of solids. In other words they have the typical syndrome of hypoadrenia which deserves to be considered and treated equally with the alimentary difficulty.

Organotherapeutic Suggestions. A few words about the organotherapy of intestinal stasis are now in order. It certainly is a helpful measure in the treatment of the natural results of alimentary toxemia and stasis. The French urge hepatic therapy as a fundamental method, as it embodies the ideal hepato-biliary stimulant, and in France *"opotherapie hepatique"* is very much more usual than here. They also routinely use adrenal extract in hypoadrenia, and combinations of these glands are used with success. It is indeed good policy to look at this side of these cases.

To tell the truth, most of my ideas concerning organotherapy and particularly the combining of synergistic gland extracts, came as a result of what I saw and heard during several visits to Paris; and one of these ideas embodied in the formula known as *Caps. Hepato-Splenic Co.* is worthy of consideration in cases such as Pauchet has mentioned. This formula (No. 5) contains two grains each of the dessicated extracts of hepatic and splenic parenchyma, half a grain of the repurified biliary salts and one grain of the first of my formulas (Adreno-Spermin Co.) which represents approximately a quarter of a grain of fresh adrenal substance, a twelfth of a grain of fresh thyroid gland and one and one-half grains each of fresh Leydig cells (from the testes) and lecithin—quite a useful "shot-gun mixture" which besides encouraging the reestablishment of the very alimentary functions which are deranged, supports the adrenal glands and exerts an antitoxic and trophogenic influence of value in modifying conditions so usually present but untreated in many cases of chronic intestinal stasis. The dose is preferably two capsules between meals three times a day for some weeks, later to be reduced to three or four capsules a day for a further period; *always as a part of a painstaking and persistent therapeutic regimen.*

Biliary Stimulation. Sometimes it may be advisable to institute more active treatment directed at the biliary stasis, in which case the *Caps. Bile Salts Co.* (S. F. No. 22) may be administered in the step-ladder fashion suggested in Chapter 13 of this section. Again the alimentary paresis may be so severe that nothing short of drastic measures must be followed out, and here it is well to give hypodermic injections of *Liquor Hypophysis U. S. P.* (Harrower). I recommend one-half a mil. daily or every other day for a week or two. It certainly stimulates the atonic intestinal musculature. Then, of course, when the hypoadrenia is decided and the systolic blood pressure especially low, 110 mm. or less (I have seen it as low as 78 mm.) the *Caps. Adreno-Spermin Co.* will favor a more normal adrenal function.

To recapitulate study the endocrine aspects of intestinal stasis. Find out if there is an associated hypothyroidism, and treat it. If the bile is deficient, help the body to make more by giving

Caps. Bile Salts Co. as advised. If the intestinal atony is marked use the posterior pituitary principle to initiate the treatment and continue it for a week or two. If there is hypoadrenia present push "the best remedy for adrenal support"—*Caps. Adreno-Spermin Co.*, giving 2 capsules with meals and at bedtime for two weeks then reduce to one, q. i. d. Later in the majority of cases the *Caps. Hepato-Splenic Co.* contains enough of the adrenal supportive elements plus the hepato-biliary stimulants to serve well, and this may be given in place of the *Adreno-Spermin Co.* and in the same dosage.

The Effects of Secretin. Still another possibility in the organotherapeutic treatment of intestinal stasis is represented by secretin bearing extracts. There may be a decided deficiency in the production of this alimentary activator, and in cases with gastric insufficiency hypochlorhydria and the resultant defective duodenal functioning, *Caps. Secretin Co.* (No. 15) has been known to be helpful. The subject is discussed in Chapter 15 of this section and special attention is called to some X-ray findings by Quimby following the use of secretin in measured cases of ileac stasis, quoted from the *New York Medical Journal,* July 24, 1915.

As a matter of fact scores of cases of intestinal stasis have been given the general and hygienic treatment with organotherapy with results which have prompted many physicians to write me their appreciation of the various formulas.

SECTION V. CHAPTER 6

THE TREATMENT OF HYPERTHYROIDISM

Hyperthyroidism is unfortunately a very common endocrine manifestation, especially in women during the period of ovarian activity, and there are three widely differing methods of treatment at present in use: (1) the thyroid is enlarged and there are a number of disconcerting symptoms, so the surgeon removes as much of it as he dares; (2) the medical treatment, which consists largely in rest, sedative drugs like the bromides, hydrobromide of quinine, chloretone, and an expectant attitude; and (3) an attempt to find the cause and control it while simultaneously neutralizing, as natural, as may be within our power, the erratic glandular dysfunction and its results.

I am not opposed to surgery, provided medicine has failed and no removable or modifiable underlying causes have been discovered, but I am most decidedly opposed to the removal of an enlarged thyroid gland when the cause of it is ignored, and when medical measures have not been applied.

The medical treatment as mentioned under the second heading does not fit in with my idea of what should be done, because the attempt is merely to control symptoms.

The last method of treatment involves three important things which have to be accomplished, viz.: (1) the control of toxemia, and especially of its serious cardiac manifestations; (2) the removal of sundry and widely differing causes of thyroid irritability; and (3) the reestablishment of the deranged chemistry and the restoration of badly disorganized nutrition.

Antagonistic Organotherapy. The immediate treatment of hyperthyroidism, in my estimation, centers upon the control of the heart, and this is accomplished quite satisfactorily by placing the patient at absolute rest in bed in a quiet room, remote from worry and noise. Suitable hydrotherapy may be also helpful. An important remedy in hyperthyroidism is the infundibular principle of the pituitary gland, and injections of a half to one mil. of my *Liq. Hypophysis (U. S. P.)* seems to exert an antagonistic effect upon some of the underlying dyscrinisms and also to slow and support the heart.

There are a number of phases of organotherapy that may be used to control the manifestations of hyperthyroidism, and let it be said that this is a very much more difficult proposition than the treatment of hypothyroidism. It is obvious that all of these patients are in a state of severe cellular irritability, and the sympathetic nervous system in particular is decidedly "on edge." The condition is technically known as "sympathetico-tonus," and it is the opposite of the condition known as "vago-tonia." (See Chapter 18 of this section.)

In all conditions of sympathetic irritability, the adrenal glands are hyperactive, and I do not believe that a case of thyroid excess exists that is not complicated by an associated hyperadrenia. If this is so, the use of the normal antagonist to the adrenal function—the pancreas—should contain within it possibilities of distinct value, and, in fact, a number of reports in the literature and many personal experiences convince me that pancreas substance (not pancreatin) has a definite sedative value in this disease.

A number of authorities have recommended pluriglandular combinations, among them Crotti of Columbus. His formula consists of equal parts (three-quarters of a grain) of adrenal, pituitary, pancreas and ovary. Several French writers recommend adrenal and pituitary, and there is a large amount of literature from which it may be gathered that dysovarism is so commonly associated with hyperthyroidism that it may be the sole causative element, and that the treatment of ovarian dysfunction may suffice to cause a marked change for the better in the thyroid manifestations.

I have been using and recommending a pluriglandular formula

containing the same ingredients as those suggested by Crotti but in somewhat different proportions. This formula is called *Caps. Pancreas Co.* (No. 6), and each capsule consists of one-half grain each of total adrenal and pituitary substance, one grain of ovary and three grains of desiccated pancreas gland. The first two may have some subtle influence upon causative elements of an endocrine character (several writers hint at this), but the chief reason for their inclusion in the formula is because of their supportive influence upon the heart, while the ovarian substance exerts its usual effect, and the generous dose of pancreas is a physiological, sympathetic sedative. This formula has been used in quite a number of cases, and its symptomatic value in many instances seems to cause just the kind of steadying needed in the cellular excitement of Graves's disease and allied disorders.

It will be recalled that the pancreas and adrenal glands are direct antagonists, and one may wonder why these antagonists are given together. I cannot answer this as easily as the question may be asked. It is possible that the adrenal gland, which includes the adrenal cortex, the so-called interrenal organ, has some influence in cases of this character, for certainly this gland has a great deal to do with the regulation of the gonads and the thyroid. Looking at it from another standpoint, it is possible that the adrenal element in this formula is useful purely for its effect upon the heart. At all events, the combination seems to be superior to the use of either adrenal substance or pituitary alone, or the use of pancreas substance alone.

The Associated Treatment. While this chapter concerns essentially the endocrine side of the subject, associated treatment is so important that it must receive attention also; in fact, a successful outcome in hyperthyroidism is the result of the appreciation of all of the involved factors and their simultaneous treatment. Obviously, sources of toxemia must be removed, and the colon is the great cause of offense. My routine treatment in such cases consists in persistent colonic flushing, oil enemas, and intelligent measures calculated to unload the colon and loosen accumulated concretions, especially at the angles of this organ. Too much attention cannot be paid to colon hygiene in hyperthyroidism. In this connection, I must refer to the frequent association of hyperthyroidism with mucus colitis, and it may be well to give consideration to the suggestions made in the chapter on that subject (Sec. V, Chap. 13). After the colon is fairly well cleaned out, regulate the diet so that it will remain as sweet as possible, using the *bacillus bulgaricus* in cultures, tablets, or cultured milk. If necessary, recommend suitable intestinal antiseptics, avoiding, however, all preparations containing iodine.

The next most common toxic cause of hyperthyroidism comes from infected tonsils or other structures in the head, including the teeth, gums and sinuses. These must be studied and treated,

if necessary, and it may be said here that all the good treatment that may be recommended in these cases will fail if an underlying cause of this character is ignored.

Other common sources of irritation of this character are pelvic infections, tuberculosis and, in fact, any hidden infective process or source of toxemia that may be subtly causing a toxemia sufficient to keep the thyroid gland perpetually irritated. Before leaving the matter of thyroid irritability, emphasis must be laid upon still one other cause of functional thyroid disorder. As we have seen elsewhere and as has been so thoroughly emphasized in the writings of Elliott of London, Cannon of Boston and Leopold Levi of Paris, the emotions exert a specific effect upon the chemistry of the body through the faculty of the adrenal glands to respond to emotional stimuli such as fright, as following an accident; fear; rage or anger; pain, and even worry. All these excite the adrenals and in this manner sensitize or irritate the entire sympathetic mechanism. In such cases, rest and the removal of these emotional tendencies must be a part of the treatment.

Another important phase of this subject concerns the relation of other glands of internal secretion to the thyroid. The most important of these are the ovaries and thymus, the former being very commonly the cause of thyroid irritability and the latter sometimes being an overlooked element in many chronic cases. In such individuals, treatment of the ovaries by surgery, medication or the X-ray must accompany such efforts as we may make for the control of thyroidism; while in the case of the thymus, it is necessary first to establish whether it is present by means of a fluoroscopic examination, and in all cases of thyroid disorder where a persistent thymus has been discovered, X-ray treatment to the thymus area should be a part of the treatment.

Finally, since the hyperthyroid individual is burning up more of herself and her food than she can afford to lose, a generous and nutritious diet must be given and special efforts taken to assure its assimilation. Incidentally, one of the reasons why pancreas gland is a useful remedy in hyperthyroidism is due to the fact that it also encourages the pancreas function, which concerns digestion (external secretion) and carbohydrate metabolism (internal secretion).

Increasing the Alkaline Reserve. All of these factors mentioned must be considered in every case of hyperthyroidism and suitable indicated treatment be carried out. Yet there is still one other thing that needs to be done almost invariably: Hyperthyroidism is very commonly associated with demineralization. The underlying causative toxic condition, besides irritating the thyroid, is robbing the body of its alkali mineral reserve in the manner outlined quite fully in Chapter 16 of this section; hence, to all of the treatment just suggested should be added the alkali

mineral salts, such as the body requires, in generous quantities to neutralize the excessive tendency to acidosis or acidemia so common in these cases.

To recapitulate: The treatment of hyperthyroidism should consist (1) in a search for causes and their removal as completely as may be possible; (2) the support of the heart and antagonizing of the sympathetic irritability, preferably by the use of the pluriglandular compound *Caps. Pancreas Co.* mentioned above (four to six capsules a day, more if it seems advisable); (3) neutralization of the tendency to acidemia and the building-up of the mineral reserve may be accomplished by the use of *Tabs. Calcium Phosphorus Co.* (see Chap. 16), of which three tablets, crushed, with at least a full glass of water an hour before food, twice a day, is a suitable dose for an adult. Finally (4), unload the colon, keep the alimentary canal as clean as possible, control the emotions, watch out for the diet, and urge a well ordered and quiet existence—in bed for several weeks or longer if necessary. Until all these procedures have been exhausted, surgery may be a failure, save only in cases of definite thyroid adenoma with thyrotoxicosis, which do not constitute a large percentage of the cases of hyperthyroidism.

I cannot fully emphasize the importance of *doing everything at once*—the organotherapy without the remineralization, the removal of toxemia, etc., is not going to be especially effective, and I may say that the reverse is equally true and many times medical and hygienic treatment which has not been causing very good effects has been made more definitely and rapidly successful by adding the organotherapeutic sedation of the sympathetic irritability as suggested here.

SECTION V. CHAPTER 7

THE DEFECTIVE CHILD AS AN ENDOCRINE PROBLEM

The problems of abnormal growth and development, especially as they relate to "children requiring special attention," as McCready calls them, constitute a very serious and difficult problem in medicine. A famous authority once said, "Throughout the animal kingdom, from the simplest micro-organisms to the most complexly organized beings, that inexhaustible power of growth has remained as one of the most remarkable phenomena of nature, the supreme riddle of life." Every so often we find a child that is "different," "backward," "defective," "abnormal," whose disabilities range from a simple tardiness in certain of

the functions of the body to a morphogenic dystrophy which has caused a material reduction in the size of the body, in its normal development, or in the power to direct it normally. Naturally the classification, "defective children," includes a very wide range of disturbances, and their consideration in a short chapter necessarily must be fragmentary.

The Endocrine Control of Growth. The burden of my remarks will concern the relation of the endocrine glands to these varying developmental disturbances, and I am convinced that they play a very important part, both in the normal out-folding of mental and physical growth and the physiological changes associated with the metamorphosis from infant to adult, as well as in the pathological modification of these changes. In other words, since the glands of internal secretion are so definitely concerned in the normal growth of the individual, we must expect to have abnormalities in these glands in the defective ones, and if the basic principles of organotherapy will hold good, we should be able to modify some of these developmental defects by applying it.

Unfortunately, organotherapy is effective chiefly in functional disturbances, and while organic conditions have been known to be favorably influenced, they are by no means as frequently benefited as the functional disorders. In the class of cases under discussion, many of the "stigmata" are obviously manifestations of an organic nature and should not be expected to be remedied; but since the underlying element is a disturbed function of some of the endocrine glands, their remarkable responsiveness to hormone stimuli may enable us to bring about almost startling organic changes, so that in this class of cases organotherapy is likely to assert a more definite influence upon structural, as well as functional, defects than in any other phase of organic disease amenable to treatment.

The miraculous changes in the athyroid cretin made possible by the administration of thyroid extract, has been one of the most magnificent advances in medicine, and it is well known that children that have the typical manifestations of hypothyroidism can be made to grow and develop in a wonderful manner by supplying the missing hormone in the form of organotherapeutic extracts. It happens, however, that hypothyroidism, pure and simple, is a rare thing, since the absence of the usual thyroid stimuli cannot but have a serious influence upon other endocrine glands ordinarily dependent upon these stimuli; hence *the cretin is never solely a thyroid case.* The same applies to disturbances of other glands, notably of the pituitary body. It has been shown that the pituitary gland asserts a remarkable influence upon growth and sexual development, and the principal manifestations of deficient pituitary function are a tendency to adiposity and sexual mal-development—the adioposogenital dystrophy of Froeh-

lich. The diagnostic side of this subject is more thoroughly considered in Section IV, Chapter 6.

Which Cases Respond to Organotherapy? The differentiation between those defective children that are likely to respond to organotherapy and those in whom there is no likelihood of benefit is a very difficult matter, and it is a most serious thing to doom a child to lifelong disability by saying that this method of prospective merit, or that, shall not be used because it is useless. As a matter of fact, case after case has come to my attention whose parents have said, "My doctor says there is no hope for Willie, because he has given him thyroid for years, and while he benefited for a while, he isn't any better in the last year or so and I am quite discouraged." In cases like this, the usual trouble is a "sin of omission." The interrelated glands have been ignored, and dependence has been placed upon thyroid alone when, in fact, the thyroid element in the case was but a part of the syndrome. Again, errors in diagnosis are possible, even by the greatest of authorities, and there has been quite considerable confusion regarding the treatment of these cases, largely because of the limited viewpoint of many observers. Now that a large amount of work has been done with the pituitary gland, the aggregate of results is beginning to be considerably better and it is hoped, as our opportunities for clinical study are enlarged, that still better results will be secured in the future.

A source of trouble concerns the determination of cerebral difficulties. If there are definite changes in the character of the cerebral cortex, or if there are developmental defects in the cranium, which naturally prevent cerebral growth and function, the prospects are not good, and many idiotic children are quite hopeless because of this particular condition. The hypocrinic child, on the other hand, is merely sluggish, not idiotic or demented, and his physiology is merely retarded and it has been shown that even the growth is not permanently arrested, which is proved by the fact that thyroid, or other organotherapy, completely changes the clinical features. There is always a possibility, however, that a child definitely defective from a cerebral standpoint may have associated with this trouble a sufficiently important endocrine phase to make it worth while to attempt to modify it, and I have come to the conclusion that it is more proper to attempt organotherapy in those cases in which the prospects are poor, than to deny the parents the "last straw" to which the proverbial drowning man clutches.

Some Results from Glandular Feeding. Since pluriglandular disturbances so generally are the rule and it has been shown that the thyroid and pituitary glands are quite often related in the causation of developmental dystrophies, it seems highly advisable to combine preparations of these glands rather than to administer them singly. I have shown in my "hypothesis of hor-

mone hunger" (Section II, Chapter 4) that a mixture of gland extracts when given to the body is made use of *in proportion to the demands,* and that it is presumable that moderate quantities of these substances that may not be needed are allowed to remain in the circulation until the time comes for their use, or they are oxidized. At all events, the pluriglandular feeding of defective children has been a good deal more successful in my hands, as well as in those of a good many of my friends, than thyroid or pituitary or thymus alone, all of which have been recommended in the literature as of use in the treatment of developmentally defective children. I have therefore combined these preparations in suitable amounts in a combination known as *Caps. Antero-Pituitary Co.* (No. 2), each dose of which contains 2 grains of the desiccated anterior lobe of the pituitary body, 1 grain of thymus, 1/12 grain of thyroid, with the mineral salts which correspond to those found in the blood. This formula has been used in many children with mental and developmental defects, and I have seen a number of cases in which it was eminently successful—of a child of two or three years, previously unable even to sit up despite thyroid feeding, who has not only learned to sit and crawl, but to walk; of children of five to seven who had never been able to speak who in six or eight months were able to make intelligible sentences of five or six words; of children of eight years who had been persistently constipated from birth and who "had never had a normal bowel movement in his life," whose alimentary conditions were modified and the constipation entirely controlled—without cathartics. (Parenthetically it may be well to state that one of the common manifestations of endocrine deficiency is cellular infiltration, muscular atonicity and asthenia, all of which very definitely favor chronic alimentary insufficiency and stasis in these cases.)

Remarkable Growth Stimulation. I have seen children who have attained the age of fifteen or sixteen, with no growth whatever for five or more years, suddenly begin to grow and change following the application of this particular formula. I recall one boy in particular who was fifteen and a half when I first saw him; height four feet four inches; general contour stubby and ugly, with a temperament that was very unfortunate—he was soured against the world and almost impossible to get along with. His liver was stimulated a little (with my *Caps. Bile-Salts Co.*, referred to elsewhere) and the *Caps. Antero-Pituitary Co.* were given, with the result that within four months he had gained two inches and, better still, his temperamental difficulties totally disappeared. I have seen infantilism in children at puberty modified by this formula or another similar to it containing extracts of the gonads also. In fact, in these grown-up children that do not mature, not merely is a satisfactory development possible, but in some of the older ones fecundity has actually

been established. Finally, a number of these peculiar children in whom the general symptom-complex included epilepsy, both of the *petit mal* and *grand mal* types, have not merely changed from a morphogenic standpoint, but the epileptic seizures have been entirely controlled. This subject is taken up more fully in the chapter entitled "Epilepsy from an Endocrine Standpoint," which follows.

Persistence Is Necessary. It is not possible to determine in advance how well this treatment may work, for medical men are not prophets and have no way of knowing exactly what endocrine disturbance is present nor how well these glands may respond to suitable stimulation. As a result of this, it is necessary to explain to parents of those who may be looking to you for help in this direction that while results have been favorable, it is not possible to predict accurately. It is the rule for these parents to ask how long it will take, and this cannot be answered definitely. They practically always ask to what degree this symptom or that may be controlled, and it is equally impossible to answer them. It is my custom to tell them that since this measure has been effective before and they have never tried it yet (for most of them come after having used a single gland extract or followed organotherapy for a few weeks or months), it is worth trying and we will hope that the results will be good. They should be told that the endocrine phase of the study of defective children is "the most hopeful side of attack by the physician"; that endocrine insufficiency has been connected with conditions similar to the one in mind; that the formula to which attention is drawn here has made many physicians pleased and brought joy to many a mother, and that it is to be hoped that in this particular case the outcome will be good also. At all events, in all these cases the real attempt is to reestablish the deficient functions—to educate certain glands; and this form of education, as with all other forms, takes time. Gland feeding must be continued for a minimum of six months. It is useless to commence unless you can secure a promise to stick to it for this length of time. It must be given regularly and the results must be watched carefully and, if necessary, the treatment modified to suit the changing conditions. Naturally, every associated effort to favor the desired outcome should be advised, and particular attention should be paid to elimination and to the metabolism of the mineral salts, an extremely important allied subject which has been carefully considered in another chapter—"The Mineral Salts in Health and Disease—Remineralization." (Section V, Chapter 16.)

The dosage is usually two or three capsules a day at meals, the former in children under six and the latter in older ones. I am in the habit of prescribing them to be taken for four out of every five weeks for at least six months. During this period of treat-

ment, if the symptoms of thyroid insufficiency predominate, I would add from ¼ to ½ grain of thyroid t. i. d.

In conclusion, I want to emphasize my position about recommending this treatment. It is a chance; it fails probably more often than it succeeds and the "successes" might not always be quite satisfactory to a critic. However, I know that its application has caused joy many times; and such joys far outweigh the failures—and they cannot be attained unless we try. It is hoped that this brief consideration of the subject may be of practical interest to those into whose hands this may come.

SECTION V. CHAPTER 8

EPILEPSY FROM AN ENDOCRINE STANDPOINT

It seems to be the custom, since the endocrine glands and their preparations have done so many wonderful things, to expect to find help from them in all the puzzles that we have failed to solve for years. This may be all very well, and occasionally we stumble over some remarkable things which keep up our courage, but when it comes to expecting a consideration of the ductless glands and organotherapy to give us the *open sesame* to the mysteries of insanity, paralysis agitans, dwarfism, sterility and epilepsy—all of them "hard nuts to crack"—it almost seems that we are asking too much. Yet the fact is that there are greater prospects today in the treatment of every one of these mentioned conditions from the endocrine standpoint than from any other procedure considered up till the present time.

It will be my effort to emphasize the importance of the disorders of the ductless glands as they may pertain to epilepsy and to suggest—not to announce—a treatment which may give us a greater degree of satisfaction in epilepsy than the unscientific and truly disgraceful method of stuffing the sufferers with bromides morning, noon and night.

Is there any relation between disturbances in the glands of internal secretion and epilepsy? If so, there may be some hope, and a statement of some of the findings in the literature may give us a reason for applying this principle in our treatment of epilepsy.

A Thyroid Factor in Epilepsy. It has been shown in many communications that disorders of the thyroid gland may be accompanied by epilepsy. In a paper entitled "The Relation of the Thyroid Gland to Epilepsy" (*Lancet-Clinic*, July 29, 1916),

I collated a good deal of information which seemed to establish the belief that hypothyroidism was a factor in the cause of epilepsy and that when an epileptic was found with an associated hypothyroidism, the treatment with obvious organotherapy—thyroid extract—might have some beneficial influence upon the epilepsy also. Gauthier, in his recent book, has gathered many communications in French medical literature, and a brief quotation from him should suffice: "Epilepsy is considered by a large number of physicians and neurologists to be an intoxication, or a general disorder of metabolism. There is also a possible connection in certain cases with the work of the thyro-parathyroid combination. The association of epilepsy with myxedematous idiocy, cretinism and even Basedow's disease is well known. But there are other evidences. Many cases of simple goiter become epileptic and goiterous mothers give birth to epileptic children. Claude and Schmiergeld, in a study of seventeen cases of epilepsy from the endocrine point of view, have found in every case alterations in the thyroid gland and in twelve of these the structure of the gland was completely altered with areas of sclerosis and limited zones of compensatory hypertrophy of the glandular tissue. . . . Parhon examined the thyroid in twelve epileptics, and found it smaller than usual and showing frequent and variable histologic changes."

From the information gathered together here and elsewhere, we are justified in drawing some conclusions:

1. That thyroid insufficiency is likely to be a frequent underlying factor in the etiology of epilepsy for several reasons: (a) It favors toxemia; (b) it produces cellular infiltration and edema, which may affect the brain in the manner described by Hertoghe, Reed and others, and (c) it usually causes other symptoms in epilepsy which have been definitely attributed to hypothyroidism.

2. Thyroid therapy is a rational therapeutic adjunct in the treatment of epilepsy accompanied by other signs of hypothyroidism.

3. Favorable results from the use of thyroid extract in epilepsy should be considered as a confirmation of these conclusions.

Involvement of the Pituitary Gland. Still another gland of internal secretion has something quite definite to do with epilepsy. This is the pituitary gland, a mysterious organ which regulates many functions of the body and about which practically all our knowledge has been developed in the last fifteen or twenty years. Just why the pituitary should cause epilepsy does not seem to be very clear save only as increased intra-cranial pressure from an enlarged gland might cause pressure upon local structures which, in turn, might cause the typical experiences which we call epilepsy. Some writers have thought that the circulatory disorders quite common in epilepsy—slow pulse, vasomotor stasis, low blood pressure, with a tendency towards obesity and an

abnormal appetite,—are somewhat similar to conditions which obtain when there is well defined pituitary disease. Harvey Cushing, the world's best authority on the pituitary gland, gives six reasons why pituitary insufficiency is related to epilepsy. In brief they are as follows: (1) Horsley, of London, noted increased excitability of the motor cortex in hypophysectomised dogs. (2) Epileptiform convulsions were frequently seen in animals which survived for long periods after partial removal of the pituitary. (Cushing.) (3) "Epilepsy is a frequent accompaniment of clinical conditions in which an insufficiency of the pituitary is manifest." (4) The pituitary may be damaged from a bursting fracture of the base of the skull. (5) It is believed the posterior lobe secretion enters the spinal fluid, thereby bathing the cortex with a substance essential to the functional stability of the cortical cells. (6) "Many individuals, supposed to be suffering from so-called genuine epilepsy, present symptoms of pituitary insufficiency and in some of these pituitary extract has served to moderate the seizures." Based upon these conclusions, a good deal of experimental gland feeding has been done in epileptics, and certainly far better results have been obtained than before this matter was given consideration.

Adrenal Irritability. Still further study of epilepsy has involved other glands, and Cotton, at the New Jersey State Hospital, has come to the conclusion that there may be an unusual irritability of the sympathetic system due to the action upon the adrenal glands of poisonous products from the intestines. Further, according to Cotton, adrenal activity also may be caused by (1) pituitary dysfunction, (2) pancreas dysfunction, (3) irritation of the duodenum, and (4) severe fright or emotional disturbances. His idea was to antagonize the adrenal irritation by the use of the normal antagonist to these glands—the pancreas —and preparations of this character have had "a decided effect in stopping the convulsions."

That there is an ovarian cause of epilepsy has long since been presumed since this disease so often may be exaggerated or precipitated in connection with the menstrual experiences. Dysovarism is known to cause a serious change in the other endocrine glands (and to be caused by such changes), and it is entirely possible that the epileptic seizures occasionally found associated with the menstrual experiences are really due to the effects upon the thyroid and pituitary, both of which are intimately related to the sex glands.

Possibly other glands have been connected with epilepsy, but in order not to complicate an already complex matter we will confine our study to the propositions already discussed.

Evidently there are several underlying or exciting causes of epilepsy that are connected with the glands of internal secretion, and whenever it is possible to discover some endocrine disturb-

ance in an epileptic, the rational thing to do is to attempt to modify it as quickly as possible. Unfortunately, however, we cannot always assure ourselves of the presence of these disturbances and the patients have well defined epilepsy and want help, and I am sorry to say that most of us heretofore have been giving nerve paralysants or sedatives as recommended in the text books. "What else is there that we can do, anyway?"

I believe that it is no more unscientific to presume that a given endocrine disturbance may be the underlying cause of epilepsy and to treat it experimentally, than it is to fill the patient up with a drug that we know perfectly well does not go to the bottom of matters and, worse still, is insidiously destroying functions (especially mental) which may not be restored once definitely damaged.

The Endocrine Element. I do not think that it is unscientific to "jump a ditch" once in a while or, in other words, to attempt to accomplish some end in a manner that we cannot accurately explain or predict the outcome of. This means that *I believe that endocrine disturbances are sufficiently commonly associated with epilepsy to warrant our using means ordinarily applied in the treatment of these endocrine disturbances as a part of the treatment of such cases.* If the motor excitability is tremendous, we must use sedatives just as we use an anesthetic in eclampsia, but always as a part of a treatment which has a greater prospect of results than the sedative itself alone.

How are we to know what glands to give in epilepsy? Several phases of the subject are mentioned and they seem to differ quite considerably. It is not difficult to establish the fact that a given individual is suffering from thyroid insufficiency. If it may not have reached the stage of the usual symptomatology, there can be no objection to using Harrower's "Thyroid Function Test" (Sec. IV, Chap. 4) and seeing how the individual reacts to this. We have no way of connecting the pituitary gland with a given case of epilepsy save by the usual study and examination (Sec. IV, Chap. 6) and, perhaps, the administration of the gland on a chance. The condition of adrenal irritation discussed above properly may be treated by the removal of all causes of this condition, especially toxemia, by antagonizing the adrenals, if it seems advisable, in harmony with Cotton's suggestion, and particularly by increasing oxidation by enhancing thyroid and pituitary function so that the accumulation of poison will not drive the adrenals so hard.

Success in Ovarian Epilepsy. Finally, in cases where there is an ovarian element, instead of treating the epilepsy, try to regulate the ovarian condition. I have several interesting cases on my records, one of which may be mentioned here: A physician had a case of epilepsy which was not responding to treatment. After a long time, it seemed that there might be some

relation between the convulsions and the ovarian function, and my *Caps. Thyro-Ovarian Co.* were given. The physician writes me as follows: "My patient, Mrs. C., age 45, had for the past five years been suffering with headache and epilepsy. These fainting spells made their first appearance after a miscarriage and have kept increasing in number until it was not unusual for her to have six, eight or even more a day. Various remedies were tried without much effect until I put her on your Thyro-Ovarian Compound and the results have been most surprising. The patient tells me she has not had one attack since starting this treatment, which naturally pleases me very greatly." Evidently this patient had a well defined dysovarism which, when treated, so modified the chemistry and nervous susceptibility that the attacks were controlled.

Pluriglandular Therapy. To return to the glandular treatment of epilepsy, *per se*. For some time I have been using and suggesting the use of a preparation made in this laboratory for the treatment of children requiring special attention—backward children, dwarfs, cretins, mongols and other developmental conditions of endocrine origin in children. This formula named *Caps. Antero-Pituitary Co.*, contains a generous dose of anterior pituitary substance, a small dose of thyroid, and one grain of thymus gland, and while this was not originally thought of as a remedy for epilepsy, it has been used in a number of cases until quite considerable confidence has been established in it and many reports have come to me, telling of excellent results obtained from its use. Certainly there are references enough in the literature to the value of pituitary treatment in epilepsy and of thyroid treatment, and, strange to say, there are records also that thymus gland alone has been used in Italy for the treatment of this condition on the supposition that there was a disturbance in calcium metabolism that might be remedied by the use of thymus. Parenthetically, it has also been used with good results in the treatment of chorea, a condition somewhat similar to epilepsy.

Suffice it to say that this pluriglandular formula, *Caps. Antero-Pituitary Co.*, has been used in epilepsy, especially in children, with very satisfactory results, and to establish this the more, I will quote from one letter: "To show you that I believed in what you were doing is but to mention that in the last five months I have been using your preparations and I have practically cured nearly 20 cases (of epilepsy) and in general have been meeting with almost unbelievable success. One case in particular will interest you: I saw this boy while he was suffering the rigors of influenza, and after treating him for this for a few days, his mother asked if I would not try to help his epilepsy. At this time the child was having 15 to 30 convulsions a day, both the *grand* and *petit mal*. The situation did not look good to me, as he had been seen by nine nerve men who had given the mother

no hope whatever. He had been circumcised and had had the tonsils and adenoids removed a year prior and had been on a diet and bromided so that he had almost no life in him.

"I modified the diet, cleaned him out some more and gave one of your combinations, and from the first week of this treatment to date, he has had no return of the symptoms, the only trouble being that from a pallid invalid he has changed into the worst youngster in the neighborhood! This I consider my most remarkable case, for it seemed like a miracle to cure this child."

I have personally seen three cases of epilepsy or *petit mal* in children that were decidedly benefited by the administration of this formula. If any of these little folks had been in my family or yours, doctor, we would have had a perfectly satisfactory conversion as to the possibilities of this method and, when opportunity afforded, would certainly have felt like giving another case the benefit of the chance that this experience might be duplicated.

I do not wish it to be understood that I am recommending this formula, or any glandular extract, as a "cure" for epilepsy or anything else. I merely state that it has been used with distinct benefit in a number of cases; that there is enough in the literature, a small part of which I have collated, to give some sort of a reason for this method of treatment, and, finally, since the prospects are so poor anyway, and there is a chance from this treatment, why not give it since two or three capsules a day are not known to have caused any detrimental effects and certainly cannot be compared to the use of the bromides? Unfortunately, not every case is going to respond to this treatment, but one single success will outweigh a hundred failures.

The usual dose for small children is two capsules a day, while to children above five years, two or three a day is proper. Individuals with well defined thyroid insufficiency may need additional thyroid extract. It is useless to start this treatment unless it is accompanied by proper dietetic, hygienic, and especially eliminative, treatment. It must be continued for months, and I am in the habit of prescribing the capsules for four out of every five weeks.

SECTION V. CHAPTER 9

HEMOGLOBIN: A REMEDY FOR ANEMIA

One of the oldest forms of organotherapy was represented by the treatment of various affections by using fresh blood from various animals and birds. As late as twenty or twenty-five

years ago, this treatment of anemia, and especially tuberculosis, was quite a common prescription; and despite their repugnance, the patients made their daily trips to the abattoirs in order to drink the blood warm from the animal. The development of a technique in organotherapy, and especially vacuum methods of drying, have put an end to all this, and repurified oxyhemoglobin in powder or solution is now available.

Some Physiological Considerations. Hemoglobin, or oxyhemoglobin, is the respiratory element in the red blood cell and is the principal source of iron in the body. The richness of the hemoglobin in the cell, and consequently the richness of the iron in the blood, controls the "respiratory value" of the blood or, in other words, determines its value as a means of taking oxygen from the air to the various tissues and bringing back carbon dioxide for elimination. Modifications in the hemoglobin content in the blood necessarily must be of serious moment, and the condition known as anemia is not merely a disturbance of the number of blood cells but of their hemoglobin content.

For many years, metallic iron (reduced iron) and various salts of iron have been recommended for their "hematinic" value, and among the better known of these is Blaud's mass, containing carbonate of iron; ferric chloride, usually given in the form of the tincture, and a large number of so-called "organic" forms of iron in which iron has been combined with proteids like casein, albumen, etc.

A great deal of experimental work has been done to determine the physiological availability of the iron in various iron preparations, and it has been shown that the majority of practically all of them, both organic and inorganic, is largely passed out in the stools unchanged or, at least, in the form of sulphide of iron. Despite this, iron is still a watchword in the treatment of anemia, and the development of our information regarding hemoglobin as a substitute for other forms of iron has shown that it is a remarkable remedy and superior to the long list of iron preparations, both in and out of the pharmacopeias. Our practical knowledge of the clinical value of hemoglobin preparations is largely the result of the clinical experiences of Hayem, Dujardin-Beaumetz and Simon, three eminent Frenchmen, and there is a large literature upon the subject.

Castellino's Clinical Conclusions. The following conclusions have been set down in a comprehensive study of this subject, which was published a number of years ago by Castellino. They still apply with equal force today:

"The absorption of hemoglobin is brought about very rapidly. It is well tolerated, even in subjects suffering from digestive difficulties, and never produces phenomena of intolerance, such as vomiting, constipation, epigastric discomfort, pyrosis, etc. Its favorable action upon the reconstitution of the blood is shown

in the increase of the number of red cells, of their resistance, weight, color, diameter, and their capacity to attain a normal appearance.

"Under the influence of hemoglobin therapy, the general health is benefited, the appetite is increased, the nutrition is better, and there is an increase in weight and strength, with a simultaneous disappearance of the various subjective phenomena of anemia. In cases of secondary anemia, as in cancer, leukemia, etc., there is a benefit obtainable from the use of hemoglobin but the result is transitory.

"Hemoglobin is indicated especially in those cases of anemia in which there are serious digestive disturbances and malnutrition, as well as in convalescence following febrile disorders and chronic disease. In order to secure the most satisfactory results, it is advisable to give a minimum daily dose of 20 centigrams. The therapeutic indications may be given: Post-hemorrhagic anemia, metrorrhagia, anemias of infectious origin, chlorosis, tuberculosis in a special manner, chronic forms of paludism, and, above all, in conditions of an acute character where there is a marked destruction of the red cells."

The Routine Value of Hemoglobin. From the above remarks, it will be clear that hemoglobin indeed has a place in the routine practice of medicine for it is a proteid-iron molecule that is easily assimilable and non-constipating. It is the most satisfactory form of iron available in therapeutics and is used and recommended as a rational substitute for various better known preparations of iron, and repeatedly has been claimed to be unsurpassed for the administration of iron by mouth.

Personally, I am inclined to believe that hypodermic injections of cacodylate of iron may be a better hematinic measure in the so-called "acute anemias"—those rapidly developed conditions of anemia due to various toxic and nutritional derangements. In such cases, however, the injections properly may be supplemented by hemoglobin, which is a much more convenient remedy in conditions where hypodermics are not acceptable and, especially, where the anemia is not so sudden nor so immediately serious.

According to Potter (Materia Medica, 13th Ed.), "the action of iron is to cause an increase of the hemoglobin of the red blood corpuscles, either by its direct conversion into an ingredient of hemoglobin or by stimulating the functional activity of the hemopoietic organs, or perhaps by both means combined. This power of enriching the red blood corpuscles by hemoglobin is essentially the whole constitutional action of iron."

Naturally it was presumed by those who were interested in hemoglobin as a remedy of prospective merit, that it would be immediately absorbed as such and be available directly and, as is the case in all "new remedies," these statements were immediately denied. Much bandying back and forth of words en-

sued in the French literature, and, after a number of years, Paul Carnot, now Professor of Therapeutics in the University of Paris, remarked in his book (page 92) that "the clinical results appear to be in contradiction to the theoretical objections which were previously formulated." In other words, whether hemoglobin is digested and changed or no, or whether it gets into the red cell with slight modification is a technical matter which does not enter into consideration when clinical results are definitely obtained, and hemoglobin, without a doubt, is the best organic iron obtainable.

A Broader Therapeutic Effect. It is believed that hemoglobin represents, not merely a good means of administering organic iron for its ferruginous value, but according to several observers hemoglobin actually exerts a homostimulant effect comparable to the effects of other organotherapeutic products, i. e., it definitely stimulates the hemopoietic organs, just as thyroid extract stimulates the thyroid gland or adrenal substance stimulates the adrenals. This may or may not be the case; but it has been proved time and again that iron in the form of hemoglobin is not so quickly eliminated from the body as other organic forms of iron, which, of course, are superior to the mineral form of which the ferrous carbonate mass is the type.

It is claimed by some investigators that the eosinophile count is an index of the regenerative capacity of the organism and especially of the medullary substance of the long bones where red-cell production has its chief seat. With this in mind, it is interesting to note that Metzner found the eosinophile count nearly two and a half times as great in a series of hemoglobin-fed animals as compared with several controls. Certainly in simple anemias, as well as in chlorosis and secondary anemias in lesser degree, the hemoglobin index is decidedly raised following a course of hemoglobin by mouth.

Hemoglobin with Synergists. Among the earliest special experimental formulas made in this laboratory was a preparation containing hemoglobin and spleen, and one of the most interesting reports that has ever come to me followed the use of this formula in a case of anemia in an Oakland hospital. The hemoglobin figure was as low as 15% (Dare) and the red cell count between 700,000 and 800,000 per cu.mm. Naturally there was a loud hemic murmur and a considerable chance that the heart would give out, so suitable stimulation was given for this as well as the special hemoglobin formula. To make a story which lasted several weeks occupy only a few lines, the patient was discharged with a hemoglobin index of 75%, and the red cell count was 4,500,000. After a good many experiments, we hit upon the stock formula which we call No. 13, *Caps. Hemoglobin Co.*, each dose of which represents 6 grains of a mixture containing 4 grains of repurified desiccated hemoglobin from the blood

of the steer, 1 grain of desiccated spleen substance and ½ grain of nucleinic acid. The repurified hemoglobin is reinforced by the addition of nucleinic acid (nuclein) and spleen substance for several good reasons. First of all, iron does not have any special effect upon leucocytosis. Blaud's mass will not affect the white cell count, nor, for that matter, will hemoglobin; but nuclein (originally prepared from the thymus) is the most remarkable stimulant of leucocytic activity known and is used in conditions where an enhanced white cell service would be acceptable. There are many reports of its value, and many of them draw attention to the noticeable resistance-increasing effects of nuclein. It fits in splendidly with hemoglobin, and to my mind the combination is made still better by adding a suitable dose of spleen substance since this product exerts a good influence in practically all the forms of anemia.

Caps. Hemoglobin Co. (Harrower) may be given in doses of four to six a day, after meals. It is a sensible, reconstructive treatment in post-operative, post-febrile and post-partum conditions, and is suggested as a routine prescription in all anemias where the first thought is "iron."

Since the above was put forward, other "special formulas" containing hemoglobin in varied combinations have been prepared to fit into the treatment of a number of clinical conditions in which anemia is a part of the syndrome. For instance, one formula, S. F. No. 35, *Caps. Nuclein-Hemoglobin Co.*, contains a generous dose of lecithin (90-95%), nucleinic acid and spermin, with hemoglobin. Following acute infectious diseases, especially in children and young people whose powers of resistance are none too good, certain forms of "nutritive organotherapy," if we can coin this term, are particularly advantageous. Lecithin, "the most easily assimilated form of phosphorus," is indicated in such cases and the definitely established effect of nuclein (nucleinic acid) in increasing leucocytosis and the powers of resistance adds to its value. Hemoglobin is also especially valuable for its hematopoietic and reconstructive capacity. To such a splendid combination, we add a small dose of spermin (from the interstitial cells of Leydig) for its dynamic or musculo-tonic effect and we have a first class organotherapeutic reconstructant.

A preparation like this combines several purely physiological stimulative effects, all of which are especially needed following any severe illness whether acute or chronic, in young or old. This will be found far superior because more rational than the old-fashioned tonics like Beef, Iron and Wine, or I. Q. & S. A hundred capsules, given in doses of three to six capsules per day, will augment the reestablishment of those essential functions which have suffered from the fever and toxemia from which the patient is convalescing.

A number of physicians have desired to combine the adrenal-

supportive formula, *Caps. Adreno-Spermin Co.,* with hemoglobin so that it would be better suited for those asthenic individuals whose difficulties are aggravated by anemia and an associated nutritional factor. For such, the S. F. No. 68, *Caps. Spermin-Hemoglobin Co.,* is suggested, since it combines these measures in a very satisfactory manner.

SECTION V. CHAPTER 10

REDUCING HIGH BLOOD PRESSURE

From the every-day standpoint, there are two distinct types of increased blood pressure, i. e., functional and organic. Individuals with the former have a high tension as a result of temporary or permanent conditions which irritate or unduly stimulate the organs whose function it is to control the mechanism of the circulation. In the other class, the tension may not be so high but the patients are found to be suffering from arteriosclerosis, renal disease, cardiac hypertrophy and other structural changes which may be both the cause and effect of the increased tension.

There are several classifications of disorders in which changes are prominent in the blood pressure. For the moment we are not interested in these. If, however, one classifies the hypertensives into the two general categories just mentioned, the functional must be considered as the result of disordered chemistry and may respond to well directed efforts to modify this; while the organic, which are, generally speaking, only amenable to palliative treatment calculated to antagonize incidental factors rather than actually soften the vessels, reduce the size of the heart and bring about structural changes for the better, have a similar etiology but are further advanced.

The Endocrine Side of Hypertension. Not a few internists now give routine consideration to the endocrine glands in their study of these cases, while ten years ago they were hardly given a thought.

Functional hypertension many times is traceable to some disorder, usually of a toxic character, which is affecting the production of the internal secretions. For instance, adrenal irritability is certainly a prolific cause of hypertension. Then again, there is an ovarian form which is due to or associated with the menopause; and this is one of the best known forms of functional hypertension—the so-called "post-climacteric hypertension."

The conviction is rapidly growing that ductless glandular dysfunction is responsible for a majority of these purely functional cases; and, therefore, that their consideration from this stand-

point may be the beginning of a successful therapy. Are not the adrenal glands (and the endocrine glands which cooperate with them) charged with the control of the sympathetic system, and, particularly, with the regulation of the cardio-vascular functions? Should they not then receive full consideration in the clinical investigation of abnormal conditions in blood pressure, whether high or low?

A persistently low blood pressure directs attention to the adrenals, and progressive students of clinical medicine think at once of Addison's disease or the less serious form of functional hypoadrenia when a systolic tension of 100 mm. or below is encountered. But as yet we have not given sufficient thought to these glands as causes of high blood pressure, though undoubtedly increased adrenal functioning is as capable of causing it as hypoadrenia is a cause of the opposite.

We are accustomed to get immediate and lasting results from the use of pluriglandular therapy in cases of hypotension. Why not apply the same fundamental principles in the opposite condition?

Neutralizing Endocrine Irritability. Many students of endocrinology have long realized the comparatively greater difficulty of controlling conditions of hypercrinism than hypocrinism —of reducing excessive endocrine activity as compared with stimulating or augmenting deficient gland function. Just as the control of hyperthyroidism is more difficult than the control of hypothyroidism, so it is a more difficult proposition to reduce blood pressure of internal secretory origin than it is to raise it. However, we do not fold our hands in the organotherapeutic treatment of hyperthyroidism, and really find much good in suitable gland extracts (see Chapter 6 of this section); and I urge that we investigate further the possibilities of the use of "antagonistic hormones" when we have to control the form of high blood pressure which is beginning to be believed, and rightly, to be the result of hypercrinism. Here the increased adrenal function, the abnormal sympathetic irritability and the conditions that go with these states, may be amenable to organotherapy; and there has accrued much advantage, in some cases at least, in carefully applying what little we know of the subject.

Heretofore our therapeutic efforts have been largely limited to the removal of all forms of toxemia—intestinal, dietetic and focal —and this is pre-eminently right, for the purins, the toxic protein wastes of amino-acid nature, and the poisons that we love to swallow (caffeine, for instance), must be rigidly eliminated. Parenthetically, I must mention the occasional seemingly proper foodstuffs which, because of idiosyncrasy or "protein-sensitization," cause more or less serious chemical reactions in the body. These should be found out and their use stopped. All these poisonous substances must be disposed of by solution and elimination,

by neutralization or by well-advised prescribing by the physician, because they are adrenal irritants, and thus keep up a continual stimulation of the blood-pressure control.

Attention also should be called to the emotional causes of adrenal irritability which have been brought to our notice by Prof. Walter B. Cannon's discoveries, which indicate that there is a relationship between emotional stimuli and adrenal excitation. How many times has worry aggravated a case of hypertension? How many times have we seen blood pressure changes as a result of severe grief or a shock?

So we routinely detoxicate, we neutralize, we starve within reason and we purge as much as we dare; and we accomplish something, for the pressure may drop, sometimes quite encouragingly. We have removed a part of the cause and the adrenals have a better chance to resume their normal service. Why not go a step further and assist in the re-establishment of the disturbed hormone balance? May this not be done by increasing those hormones which are known to antagonize the adrenals? I think so.

Sometimes our prophylactic treatment just outlined causes the pressure to drop a notch or two and it may hover at, say, 180 or 190 mm. The regimen becomes a bit too strenuous or too monotonous and the patient tires of the diet, the medicine and the other treatment, and the pressure begins to increase again. It is here that organotherapy may render the most efficient service.

Pancreas Gland a Remedy for Hypertension. I believe that pancreatic organotherapy favors the control of functional hypertension, both by increasing intestinal digestion as a result of its effect upon the pancreatic external secretion and by its direct anti-adrenal action so well described in the literature and so often proved by experiment and clinical application. This is due to the homostimulant effect on the internal secretory capacity of the pancreas, which has as two of its responsibilities the balancing of the adrenal medullary principle and the regulation of carbohydrate metabolism. Parenthetically, this reminds us of the relation of pancreatic diabetes to hypertension and the condition of adrenal sensitization (shown up by Loewi's test) in hyperadrenia or reduced pancreatic endocrine activity, but this is too large a subject for consideration here. It is mentioned again in Section IV, Chapters 11 and 12.

To repeat: The pancreas very definitely opposes the adrenals; and several authors have spoken well of the depressor virtues of pancreas organotherapy. We therefore will attempt to increase pancreatic activity as best we may and will hope to see results which show that adrenal hyperactivity is being reduced. Often the hypertension accompanying this condition is reduced in a salutary manner, and a diminution of 40 to 60 millimeters is no uncommon thing.

The Detoxicating Influence of the Thyroid. Another important phase of this very large subject must be mentioned ever so briefly: The thyroid is concerned chiefly in the control of the detoxicating mechanism of the body. It is the great oxidizing agent; and when its work is below par (as one would expect it to be in individuals who suffer from the functional hypertension under discussion), conditions favorable to the production of high blood pressure are allowed to establish themselves. This gives us a partial explanation for the good results which are reported in some cases of hypertension which have been treated with thyroid extract alone. In such cases, small doses of thyroid may be given with advantage for months, and the "deaminizing" effect of the thyroid hormone explained by Slosse, of Brussels, undoubtedly is helpful.

Again, waning gonad function is quite commonly connected with hypertension. It has been repeatedly stated that a part of the service rendered to the organism by the sex hormones relates to intracellular oxidation. Hence the functional recession of gonad activity naturally would tend to favor deficient metabolism and, consequently, a toxemia which must be just as irritating to the adrenals as any other form of toxemia such as has been referred to above.

Attention has been called to the frequency with which a high tension may follow the menopause. There are several interesting reports of the value of ovarian organotherapy in hypertension of this type. Most comprehensive among these is the paper by Carey Culbertson, of Chicago (*Surg., Gyn. & Obs.*, Sept., 1916), in which it is shown that vasomotor disturbances of the menopause are largely endocrine in origin—due to the withdrawal of the ovarian hormone and the discord which necessarily results for a time. These relations and the results from the dominance of this secretion or that are carefully gone into in detail in Culbertson's article. Hypertension is the rule in these cases, in fact it was present in all but four of the whole series which he reported. The fundamental cause is believed by Culbertson to be adrenal hyperactivity and perhaps a disturbance of the pituitary following the removal of the influences undoubtedly due to ovarian endocrine function. Based upon this idea, ovarian or luteal homostimulation should tend to neutralize these pressor substances, thereby reducing the tension, and this seems to be the case since Culbertson reports excellent results in many such cases.

Sanes, of Pittsburgh (*Trans. Am. Gyn. Assn.*, 1918), discussing vasomotor instability at the menopause, also speaks well of the organotherapeutic regulation of high blood pressure in cases of this character.

To conclude this short study, and to sum up:

1. Certain functional hypertensive conditions deserve to be considered from the standpoint of endocrinology.

2. These cases should be carefully selected and the organic factors eliminated.

3. After as thorough detoxication and elimination as is possible to secure and in conjunction with this treatment and preventive and dietetic and hygienic measures, I suggest organotherapy.

4. Pancreas substance is indicated. Thyroid may be useful. Ovary is of decided value in certain cases. Pluriglandular therapy has a reasonable basis and is worthy of a trial.

The Pluriglandular Treatment of Hypertension. Personally, I have been successful in reducing a number of functionally high blood pressures ranging from 165 to 245 mm. by the use of a series of pluriglandular formulas based upon the foregoing ideas; and I believe that the consideration of the subject from this viewpoint is rational and, incidentally, of a character which circumstances make it possible to measure with considerable accuracy, for here we do not depend so much upon the patient's say-so as upon sphygmomanometric figures.

During the first year of our studies in this direction, we have used eight different formulas and finally have come down to Special Formulas Nos. 29 and 30, *Caps. Thyro-Pancreas Co. with Spermin* (29 or *with Ovary* (30). Each five-grain capsule contains two grains of desiccated total pancreas gland (not pancreatin), one twelfth of a grain of U. S. P. thyroids and two grains of spermin (made from the interstitial cells of Leydig from the testes) or total ovarian substance, as the case may be. I use the former in men, the latter in women. The blood pressure reducing effects of the latter, especially at the menopause, seem to be more uniform and greater than the former. Both formulas are worth trying as a part of the therapeutics of hypertension, especially of the functional type, for high blood pressure is a dangerous proposition and there can be no likelihood of detrimental by-effects. Certainly such measures are just as rational and worthy of application as iodine in various forms or the nitrites and other vasodilators, for something of real physiological usefulness is being accomplished by the organotherapy.

Clinical Results from This Method. Some of the results have been most encouraging. From my own records, I can give several figures: A woman of 50 came with a B. P. (systolic) of 245. After one month it was 190 and after two months it was 172. She is evidently much improved. Another woman at the menopause took the capsules (S. F. No. 30) for about a month; the tension was reduced from 185 mm. to 155 mm. A gentleman followed my suggestion for less than a month, i.e., he cut out coffee, took an alophen pill every other night (on general principles) and the S. F. No. 29 q.i.d. His tension was reduced from 185-190 mm. to 140 mm. Still another case, using the same formula, showed a reduction of 40 points when the seemingly irreducible minimum was 190 mm. Many reports have been made

to me personally and by letter. I can mention a few of these figures off-hand: 210-160; 180-135; 200-145; 185-140; and 220-175. All these figures refer to the systolic pressure, for it happens that functional high blood pressure usually concerns more the systolic rather than the diastolic figures.

We cannot definitely promise any uniform results from the treatment, for the value of this method depends a great deal upon the conditions present and, especially, the responsiveness of the endocrine glands. The *raison d'être* is quite logical, and the percentage of results is high enough to raise our hopes. It is a measure which to my way of thinking far outclasses the nitrites, iodides and other half-way measures routinely used in this common condition.

SECTION V. CHAPTER 11

ORGANOTHERAPY IN PROSTATIC DISORDERS

The prostate gland is one of the least understood glands of the body, at least insofar as any possible internal secretory function that it may have is concerned, and in regard to its relation to the other endocrine organs and especially the gonads. Information regarding the experimental effects of prostate extracts and of the use of prostate preparations in clinical practice indicate that certain therapeutic possibilities are enfolded in this gland, but the subject is by no means well understood and this statement necessarily must be incomplete and to a certain degree indecisive.

Certain clinical disturbances of the prostate undoubtedly are associated with the sex manifestations, and it is fair to presume that the prostate is involved in the reproductive function in a considerably broader manner than its production of the seminal plasma.

Prostate Hypertrophy as a Compensatory Manifestation. The fact that prostate hypertrophy quite commonly follows the functional retirement of the testes would indicate that there might be some relationship between the endocrine activities of both of these glands. It has been suggested that there may even be a friendly hyperactivity of the prostate; that is, when the testes become functionally inactive, the prostate may be enlarged in a compensatory fashion just as we know various other ductless glands may enlarge when other closely related endocrine organs are put out of commission. At least, we know that, provided we can exclude deepseated and overlooked infective processes and essential new growths of the gland such as adenoma or cancer, there evidently is a form of enlargement of the prostate connected with waning gonad function which, theoretically, ought

to respond to an organotherapy which would supplement the endocrine function of the testes and thereby lessen the probable necessity for overactivity on the part of the prostate. The idea of a compensatory prostatic hypertrophy is not yet a proposition accepted by urologists, but the treatment of it, based upon the outlined idea, has been most encouraging. In conjunction with several prominent genito-urinary specialists, a special formula has been developed in my laboratory, called *Caps. Leydig-Cell Co.* (S. F. No. 41), the essential basis of which is an extract of the interstitial cells of Leydig, undoubtedly a useful organotherapeutic remedy since these cells are the essential structure of the sex glands. (It has been even hinted that these cells properly might correspond to a "male corpus luteum.")

Hypoprostatism and Neurasthenia. A number of reports in the literature, as usual especially in French, state that there is a therapeutic value inherent in desiccated prostate substance, that it meets the expectations of a homostimulant gland extract and is therefore likely to be valuable in conditions of prostatic insufficiency. It has been recommended chiefly as a remedy in the neurasthenic manifestations accompanying prostatic disease and following prostatectomy, and as an advantageous addition to the Brown-Sequard method of treatment for presenility, impotence and certain functional sex neuroses. Laignel-Lavastine, a famous Parisian neurologist, tells of good results from this procedure, and Beard, Blanche and others agree with him.

To meet a demand for a preparation of this character, S. F. No. 48, *Caps. Prostate Co.*, has been prepared, each of which contains 1½ grains each of the desiccated prostate substance, interstitial cells of Leydig (spermin extract) and lymphatic gland substance, together with an effective dose of nucleinic acid. The latter is added because of its leucocyto-stimulant effect and its well known value in conditions of lowered resistance where infections are or have been involved.

Last year, I had a personal experience with this form of treatment which was quite encouraging. The patient, an old soldier-chaplain, age 81, was sent to me in the hope that something might be done to relieve him, for after long periods of treatment for prostatic and urinary difficulties he was in a deplorable state. I am not a genito-urinary man, and hesitated to have anything to do with such a case. He had a very much enlarged prostate, much urinary difficulty and a most obstinate form of constipation. He was very old and frail, with a bad heart and no leaning to surgery. I therefore advised the *Caps. Prostate Co.* on what I called "half a chance." Here is a report which he made some months later: "I am much better. There seems to be more 'pep' to the contractile force of the bowel and less obstruction to the passage of feces. A noteworthy point is that the diameter of the stool is much larger during each course of the capsules.

The difficulty with urination is almost gone, and with two or three short exceptions I have had none of the troubles of this nature (dysuria and frequent micturition)." In this case, there was a decided reduction in prostatic size and tenderness; the results were doubly remarkable because of the age and condition of the patient.

A Prostatic Form of Impotence. Another practical application of prostatic organotherapy was first suggested by Bazy. He found it valuable in "prostatic impotence"—that form of sex debility in which prostatic hypertrophy and hyperesthesia was or had been prominent. Usually these cases have suffered from emissions, premature ejaculation and the usual host of neuropsychoses of the "sexual neurasthenic." In developing these notions, Reinert found that such chronic prostatic enlargements were reduced and that simultaneously urinary retention and tenesmus were diminished, while in younger cases there was occasionally excellent control of the hyperesthesia and its associated

Still another preparation of this character made in my laboratory has been the subject of considerable recent study and clinical application. Under the name *Caps. Gonad Co.* (S. F. No. 70), a combination similar to the last but containing in addition an extract of the anterior lobe of the pituitary gland, has been made and used chiefly for the attempted re-establishment of lost sexual powers, with an aggregate of results which has made a number of those using it remark that "it is the most effective thing that I have ever used or recommended." This particular phase of organotherapy, which is a considerable advance over the original Sequardian measure, is more thoroughly discussed in the following chapter, "The Hormones in Impotence."

In closing, it should be remembered that glandular extracts of the character under consideration exert a specific influence upon the glands to which they correspond and must not be expected to develop results beyond their scope. The endocrine function of the testes is not, by any means, its spermatogenic function, though doubtless they are related, and the re-establishment of the gonad endocrine function does not necessarily involve the restoration of fecundity. It seems, however, that the ductless glands involved in the generative process, aside from the gonads or essential sex glands, exert a paramount influence upon the effectiveness of these organs; and it has been shown many times that aspermia, as well as Leydig cell incompetence, has been re-established by thyroid or pituitary medication, hence the inclusion of preparations of this character in a remedy from which one expects tonic qualities is in order, the more especially when the importance of the anterior lobe of the pituitary is remembered in connection with gonad development, as emphasized by Froehlich, Bartels, Cushing and many others.

There has been a good deal of skepticism in regard to the

value of preparations of the prostate gland and allied organs. In many instances, this skepticism has been changed to enthusiasm by clinical experiences, but it is very important to remember that the endocrine side of these cases—the side that is likely to be affected by this kind of treatment—is by no means the whole thing, for, unfortunately, many times there is an important psychic aspect, and all the most effective forms of organotherapy will not remedy this—any more than they will control an overlooked infection.

SECTION V. CHAPTER 12

THE HORMONES IN IMPOTENCE

It was in the year 1888, or thereabouts, that Prof. Browne-Sequard, working in his laboratory in Paris, proved on himself a remarkable effect following the injection of a preparation made from the testes of a dog. His report was made to the Academie de Medicine and published in his own *"Archives de Physiologie"* (1889, xxvi, 651; also p. 739). This was the beginning of scientific testicular organotherapy.

Unfortunately, as a result of the attitude of the Parisian charlatans, who promptly seized upon Browne-Sequard's announcement with avidity, seeing therein a chance to mulct their susceptible cases of still more money, the whole subject fell into disrepute because the noise made by the charlatans drowned out the real, scientific statements of the famous physiologist and his co-workers, especially D'Arsonval. This "black-eye" has always stayed with this form of organotherapy. Physicians subconsciously feel that testicular opotherapy "savors of quackery." Nevertheless, the fundamental principle proved by Browne-Sequard on his own body and duplicated times innumerable by other reputable physicians is as sound as any other phase of gland medication.

The Dynamogenic Effect of Spermin. The two essential facts about this form of treatment are: (1) It increases dynamos—muscular, nervous and sexual, and (2) it homostimulates the gonads, just as extracts of other endocrine glands exert a stimulating effect upon the organs corresponding to those from which they were made. Browne-Sequard found that his mental and physical vigor was much increased. In his own words: "Considerable laboratory work hardly produced any fatigue, and to the astonishment of my two assistants I was able to work for several hours in a standing position." Dynamometric experiments proved this muscular effect in figures. They have been made since and ergographic curves have also been made, and

both register definite dynamic increases following this form of organotherapy. This same treatment also stimulates oxidation and appears to favor a better cell chemistry. A number of years later Prof. von Poehl, of Petrograd, isolated a crystalline principle which he called "spermine," from testicular extract. It is believed to be the essential stimulating principle in this extract, and there is a large literature upon its pharmaco-dynamic influence.

A good deal has been written on the subject and, naturally, there have been many adverse criticisms. These have been largely based, to my way of thinking, upon the foundation to which I have already referred and on the failures which inevitably must follow the use of such a measure when the fundamental causes are ignored and the treatment is continued only for a limited time. The fact is that two-thirds of the unkind things said about organotherapy have been based on half-way work and the setting of one's hopes too high, and testicular organotherapy is the one form of gland feeding upon which great expectations are placed. The senile and the roué both long for the re-establishment of their lost powers. They do not deserve to recover them, for they have been misused; and just as the alcoholic's liver is most obstinate to the best of treatment, so the gonads of his associates cannot live up to the abnormal demands made upon them and may not respond to the best of treatment.

This is the unfortunate side of this matter, for in no other phase of organotherapy is so much expected and so little deserved. Despite this, the underlying principle of organotherapy remains unchanged and the law of homostimulation still applies. So, provided that circumstances can be made half-way favorable, there is greater hope for the re-establishment of gonad endocrine function from organotherapy than from all the phosphorus, the damiana and the nux in the world; for hormone therapy has one great thing in its favor,—it is a natural method.

Developing a Pluriglandular Sex Stimulant. From the beginning of our work out here in Glendale, we have been importuned frequently to "give us something along this line for these played-out wrecks we so often meet." Several interested genito-urinary specialists have taken up the matter with us; and a number of tentative special formulas have been made, to one of which your attention is called here. Let it be said here in no uncertain terms that we have not discovered a "cure for lost manhood." We know too well that this will never emanate from any laboratory, for the personal factor far transcends the physiologic. However, we really feel that something worth while is being accomplished, which seems well established by the encouraging letters and appreciative comments which reach this laboratory from month to month.

A pluriglandular formula, which was the seventieth experimental preparation made in this laboratory (S. F. No. 70, *Caps. Gonad Comp.*), was originated in conjunction with a Brooklyn, N. Y., urologist who has given the subject much study and practical investigation. He argues—and I most thoroughly agree with him—that the preparation of the essential endocrine cells of the testes (the interstitial cells of Leydig, as they are called) does homostimulate the corresponding cells in those to whom it is given. In such cases, the addition of other synergistic gland extracts should be helpful, for the same reason that combinations of various endocrine products excel single extracts which may be indicated in other disorders. Among the most obviously helpful of these synergists are the anterior pituitary gland, the thyroid, the prostate and the lymphatic glands, for reasons which are sketched below.

The Endocrines which Cooperate with the Gonads. It is well known that the essential endocrine part of the pituitary body (the anterior or glandular lobe) exerts a gonad-stimulating effect. Recall the adiposogenital dystrophy of hypopituitarism where sexual function is lost and atrophy of the sex organs is a pathognomonic finding. Further, the clinical use of anterior pituitary feeding by Stellwagen (*N. Y. Med. Jour.*, Nov. 4, 1916), and others is reported to be effective in impotence.

Again, hypothyroidism usually accompanies hypogonadism, whether in the male or female. The cretin does not develop sexually. Further, in conditions of cell-laziness and senility, as well as in conditions where the gonads are below par, so also is the thyroid. This is both a causative and a resultant factor; and I believe that a small dose of thyroid is an eminently suitable remedy for the hypothyroid manifestations of the asexual as well as in the elderly individuals whose hormonic functions are on the wane. It is incidentally interesting to remark that DeLee, of Chicago, and other obstetricians admit in their writings that thyroid medication has been efficacious in the control of sterility in women; and, as I see it, for the same fundamental reasons it is useful in men.

The prostate is indeed a gland which has some broader physiologic influence than the production of its seminal secretion. Many writers believe that it is a real endocrine organ; and experience shows that to add prostatic extract to the other gonadostimulant extracts (as, for instance, those just mentioned) is worth while, especially where there is a prostatic factor in the syndrome it is desired to modify. (See "Organotherapy in Prostatic Disorders," Chap. II of this Section.)

Clinical Success with This Method. Suffice it to say that the *Caps. Gonad Co.*, has been used in several hundred cases as a means of re-establishing lost or deficient gonad function with real success in a sufficiently large number to warrant its

recommendation. It has served its purpose many times, where previous treatment—local, psychic and general—has been tried for months and has failed. It is a gonad stimulant, even though I do not believe it will replace worn-out organs or reduce the age of those who may be induced to take it! Naturally, most of the cases in which it has been used so far are old, chronic cases who have not previously responded to the usual treatment. I am assured that some of them had long since been given up—just as the individual with the sexual atrophy and dysfunction of real hypopituitarism discovers that he is permanently impotent, though actually he may recover a part or all of the lacking faculties following pituitary feeding, just as amenorrhea has responded to ovarian therapy or the unsightly cretin can be made to grow and develop after prolonged thyroid feeding.

This all puts a new and more encouraging aspect upon a subject which is unfortunate, to say the least. The prospects are better than heretofore; even if we have not found Ponce de Leon's long-sought elixir!

Caps. Gonad Comp. is given in doses of three to six capsules a day, usually for some weeks or months. It should be given as a part of the treatment of a given case. Causative factors—infective or psychic—should be controlled, for obviously no form of therapeutics not directed at these could be expected to be resultful.

This treatment is admittedly experimental—and always will be, for it is unlikely that we can accurately label a given case and ascertain beforehand whether or not the endocrine factor is prominent and the organs responsive to hormone therapy. The chief "experiment" was not so much to establish the essential effects of organotherapy—we already know something about these—but to broaden them by making the right combination. This particular formula is the result of many trials, is based upon principles which are sound, and is certainly more effective than orchic extracts alone. Already its administration has secured satisfactory results where long periods of such treatment had failed. To say the least, it is worth considering, especially when both physician and patient usually are decidedly "up against it," as is so often the case in such conditions.

SECTION V. CHAPTER 13

THE MUCINASE THEORY IN MUCOUS COLITIS

For a long time it was supposed that the real, underlying cause of mucous entero-colitis was a nervous one, and that neurasthenia was intimately connected with the causation of this

common and intractable condition. Personally I am not convinced that this is so, rather I believe that the neurasthenia so often accompanying mucous colitis is a result of the combination of conditions, not a cause of it.

About ten years ago some very interesting work on mucous colitis was done in France by Professor Roger and his associates. Like many a really good thing, the ocean seemed to prevent its reaching us in this country, and while in all these years "the mucinase theory" has been put to practical use quite commonly abroad, here it is still the rule to muddle along with our cases of mucous colitis as best we can.

Mucinase and the Coagulation of Mucin. Briefly, the idea is this: The intestinal walls normally secrete a ferment named by Roger "mucinase," the function of which is to coagulate mucin. This ferment is rendered inactive by certain alcohol-soluble, heat stable substances in the bile, and Roger inferred that, since the disease was so often associated with biliary insufficiency and experimentally produced by diverting the bile flow from the duodenum, the membrance formation was due to insufficiency of bile. Later Riva actually isolated and identified mucinase in the feces of patients with this disease. Nepper and others have proved this both clinically and experimentally, and he has come to the conclusion from his clinical results that mucous colitis is due to what he calls *"oligocholie"* (bile insufficiency) and cannot exist without it, and that the membrane formation is due to the abnormal increase in the ferment mucinase and to a relative and simultaneous diminution in the production of the bile, especially as regards its anti-coagulating power, which permits the mucinase secreted by the intestinal epithelium to assert its coagulating powers.

All of this explains the following statement quoted from Roger's book on the disorders of digestion: "For those who pass membranes, prescribe an extract of ox-gall, and you will frequently see a subsidence of the pain and a complete disappearance of the membranous casts."

Whether it is true that the bile plays such an intimately important role in the causation of mucous colitis, or not, is a matter of technical interest. We know full well that the production of mucous, the resultant intestinal irritation and toxemia and the final tenesmus and discomfort during the "spells" of loosening the bacteria-ridden mucous poultice which covers so much of the intestinal area and the general malaise are always accompanied by symptoms attributable to hepatic torpor and biliary insufficiency. I do not recall of ever having seen a case of mucous colitis where I felt that the production of bile was normal.

Many colitic patients need cathartics during the periods which intervene between their "spells," and all of them are toxic and have a very foul alimentary condition. If, instead of having

recourse to the usual cathartic remedies, we would use "the most natural cathartic known"—bile—we might be doing something of direct physiologic service to the patient, for in addition to its chologogue and cathartic value, the bile carries with it a subtle something that neutralizes the ferment which favors the coagulation of mucin.

A Routine Method of Treatment. This is not a theory; for it has been put to splendid use in practice and I am going to suggest a routine method which may stand many of my correspondents in good stead in some chronic case which has "been the rounds" with little or no help:

First clean out the bowel by judicious catharsis, a very limited diet for a day or two, cleansing enemata—sometimes a hypertonic saline enema loosens the mucous nicely—and the use of high oil injections (four ozs. of cottonseed oil preferably containing 10% of Isarol) to be retained all night for, say, three nights in succession. Administer generous doses of your favorite intestinal antiseptic—the sulphocarbolates, iodine in proper form, bismuth betanaphthol or salol—and get a decent start.

Then prescribe a non-toxic diet with the easily putrefiable proteids reduced to a minimum (no bran, cellulose or mechanical irritants) and the known-to-irritate foods (all these cases will tell of some special foods that cause unusual trouble) eliminated entirely.

Then give bile and encourage the hepato-biliary function to the limit. I suggest my S. F. No. 22, *Caps. Bile Salts Co.,* each capsule of which contains three grains each of repurified powdered biliary salts and of desiccated hepatic parenchyma. Give it in step-ladder doses as follows: Prescribe one capsule three times a day between meals for two or three days, then increase by adding an extra capsule to the last dose, then still another capsule until the patient at the end of a couple of weeks is taking, perhaps, three capsules three times a day. The signal to reduce the dosage is the presence of free bile accompanying the stools, and the patient should be requested to watch for the yellow-green bile floating upon the water in the toilet. When this appears, irrespective of the dose that may be being taken at that time, reduce the dose to the original one capsule, three times a day, and start up the ladder again, either at the same rate (increasing the dose every 2 or 3 days) or at longer intervals. Have this procedure continued for several months, or modify it as suggested below, the while giving the patient some acceptable form of the *B. Bulgaricus.* (I have been in the habit of prescribing a very active and convenient fresh culture made by the Vitalait Laboratory of Pasadena—they send it out twice a week in tubes and charge for it by the month.)

The Relation of Secretin to Mucous Colitis. There is another angle to the subject which should be mentioned. While

the Roger-Nepper idea is sound and practical, it may occur to us to question why there is a biliary insufficiency, with corresponding reduction in the production of mucinase, etc. There are several fundamental causes, one of the chief of which is gastric indigestion with deficient production of hydrochloric acid and a consequent defect in the production of secretin in the duodenum. This is a serious matter, for it has been shown that secretin activates pancreatic digestion, the functions of the intestine itself *and also the production of bile.* Hence duodenal extract (secretin) may be equally effective as bile salts, and, perhaps, even more fundamental in its influence than bile alone. It happens that *Caps. Secretin Co.* (No. 15) also contains a dose of bile salts as well as an effective amount of adrenal substance—and hypoadrenia is about the most common result of mucous colitis due to the invariable toxemia which naturally depletes the adrenals.

So one has the choice of these two preparations in the organotherapeutic part of the treatment of mucous colitis, and it is difficult to say which is most efficacious. I recommend the *Caps. Bile Salts Co.* in the step-ladder method suggested for, perhaps, a month, and then the continuation of the treatment with *Caps. Secretin Co.* for a month or more. Both may be taken together, the dosage being regulated by the effects of the total amount of bile that is given daily. The fundamentals of the physiology of secretin and some remarks about its therapeutic possibilities will be found in Chapter 15 of this Section.

It really does help. And with the experimental work of Nepper, Roger and other French investigators to give us a reasonable explanation of how it works, we need not feel that this is merely an attempt to boost some special method of treatment.

SECTION V. CHAPTER 14

MAMMARY EXTRACT IN THERAPEUTICS

Whether or not the mammary glands are really glands of internal secretion is a moot question. Some say "Yes" and prove it in a fairly intelligible manner, while others say "No"—on general principles! Certain facts indicate, however, that these glands deserve at least to be considered from this standpoint, for the mammae are under hormone control and they contain within their structure a substance which remains in the desiccated substance and which, when used as a remedy, exerts a definite action upon the mammae themselves (homostimulant), as well as upon other remote organs.

The Hormone Control of the Mammary Glands. A number of common experiences remind us of the hormone relations of the mammae: It is a well established fact that the operation of spaying dairy cows at the time of their greatest flow of milk has a distinct lengthening influence upon the lacteal period. Additional emphasis is lent by the fact that the function of ovulation is retarded and sometimes entirely stopped during prolonged lactation, presumably because in this stage of mammary activity ovarian activity is antagonized in a greater or less degree due, as some will have it, to an associated increased elaboration of the internal secretion of the mammary glands. It is also well known that the supply of milk is considerably lessened soon after a new conception takes place.

Still another aspect to this subject is worthy of passing comment: I have frequently noticed a relationship between very large mammary development and scanty menstruation. In a paper entitled "Mammary Therapeutics; The Mammae as Glands of Internal Secretion" (*Woman's Med. Jour.*, Mar., 1914), I called attention to this, and it was remarked that while this is by no means always the case, it points at least to an antagonism between the mammae and ovaries. Late in 1918, Oliver T. Osborne, of Yale University, wrote, "Girls with very large mammary glands may have long periods of amenorrhea without pregnancy, or they have very irregular or scanty menstruation."

Most of these findings, it is true, indicate that the breasts are related in some way to hormone influences, i.e., they may exert some control through an internal secretion upon the ovaries or other organs. Further proof of this activity of the mammae will be forthcoming, for, as will be shortly seen, this antagonism is made of good use in therapeutics.

Numerous references to the use of mammary extracts show conclusively that they have caused decided therapeutic effects, and at the same time emphasize the importance of what still must be called a much neglected field of therapeutics. In fact, mammary therapeutics is getting to be a well established part of organotherapy, despite denials which still are heard occasionally. The truth is that mammary substance is one of our best measures for antagonizing ovarian activity and lessening functional congestion in the pelvis.

Mammary extract is produced from the carefully desiccated parenchyma of the udders of cows, goats or ewes, and is prepared in dry form with the precautions customary in the manufacture of effective organotherapeutic preparations; and whatever the principle may be that is the cause of the therapeutic activity of this extract, it is evidently not destroyed when passing through the stomach. Incidentally, much work has been done with soluble mammary extracts given hypodermically, and they have been virtually discarded in clinical practice because

of the local pain and induration which so often follows such injections.

The Control of Menorrhagia. As has been stated, there is an antagonism between the mammae and the ovaries, and it was natural that mammary extract should be used in the attempt to overcome the results of excessive ovarian activity. Among the conditions which have been classed under this head are menorrhagia with increased uterine congestion, uterine hypertrophy and fibroid degeneration, as well as certain conditions in which there is an increased degree of functional ovarian activity, including nymphomania, etc.

A number of investigators have used this method to produce uterine depletion and to control hemorrhages shown to be due to functional causes as distinguished from those of organic origin, such as the presence of foreign bodies in the uterus, polypi, placental remains, cancer, etc. Osborne stated very recently that "profuse menstruation in girls . . . may be prevented by the administration of mammary substance." In another place, the same writer says, "A profuse or too frequent menstruation, where there is no pathological excuse, especially in young girls, may be corrected by feeding mammary extracts."

Pochon has used mammary substance and recommends it for its decided anti-hemorrhagic influence (however, it is not a styptic by any means) and calls attention to the fact that while mammary extract tends to cause uterine depletion, ovarian extracts have an entirely opposite tendency, causing an increased uterine blood supply. Battuaud indicates that this form of medication has proved valuable in the control of menorrhagia in young girls, just as it has been found serviceable in metrorrhagia of the climacteric. Congestive conditions of the ovary resulting from inflammation of the adnexa and other causes may be reduced in this manner, although, of course, the influence is more mechanical—i.e., decongestion is brought about in a chemical way and there is no particular action on the infective process. In other words, mammary extract is a valuable adjunct to treatment. Dalche, Jayle, Pozzi and other French gynecologists have expressed themselves freely as convinced of the efficacy of this method. The advantage of this depletion is obvious in pelvic congestion of varied origin. It has been used in severe pelvic pain due to infection (and consequent congestion), and even in uterine cancer with constant oozing where results have been so good—stoppage of all flow and reduction of the bad odor—that the patient has anticipated a cure, though, of course, this is not possible. Luncz, in his interesting monograph, has gathered a number of reports of benign cases in which mammary opotherapy caused an entire cessation of severe uterine hemorrhage in persons of widely varying age.

Other writers have gone further, among them Forgue and

Massabuan, who, besides demonstrating clinically the anti-hemorrhagic action of this preparation, have shown experimentally that at the menopause there frequently is an obvious increase in the corpora lutea with hypertrophy of these cells. They presume that the hemorrhages so common at this time may be due to two causes: Temporary increased production of the luteal hormone, and an associated decrease in the production of its antagonist—the mammary hormone—resulting, of course, from the usual retrogressive changes expected in the mammae at this period. This harmonizes entirely with the facts previously collated here, and is further evidence of the soundness of the position that I have taken for years and established to my own personal satisfaction that *this particular anti-hemorrhagic influence of mammary substance is indeed a pleasing reality in many cases.*

Preparations Containing Mammary Substance. Among the numerous stock and special formulas made in my laboratory are four containing mammary gland. The first of these, No. 3, *Caps. Placento-Mammary Co.*, is used chiefly as a galactagogue where the homostimulant effect of the remedy supplements the more active effect of desiccated placenta. The subject is given full consideration in Chapter 4 of this Section.

A second mammary combination is S. F. No. 38, *Caps. Mamma-Ovary Co.*, which is used in menstrual difficulties of an ovarian character which lean toward an excessive flow. This class of cases is hardly to be called menorrhagia, since the flow usually is not particularly serious. In these cases, ordinarily occurring in girls and quite young women (in contradistinction to the real menorrhagia of older women, especially at the menopause) the flow lasts six, seven or more days and may recur at shorter intervals than is normal. Here there is not so much a condition of ovarian irritability or excess as a dysovarism which is accompanied by pelvic congestion and the minor form of menorrhagia just mentioned. Because there is a decided dysfunction of the ovaries, the mammary substance is combined with a thyro-ovarian combination; and despite the known relations of these glands, the body seems to be able to use the differing stimuli simultaneously. In cases of dysovarism which tend toward a prolonged or too frequent flow, the *Caps. Mamma-Ovary Co.* may be superior to the more frequently used *Caps. Thyro-Ovarian Co.* which is considered elsewhere in this Section.

Two other formulas of this type deserve to be mentioned: These are S. F. No. 39, *Caps. Mamma-Ergotin Co.* and S. F. No. 40, *Caps. Mamma-Pituitary Co.* Both of these are used for the control of uterine bleeding, whether post-partum, climacteric, fibroid, or even in cancer. The former, made originally for a prominent Oakland obstetrician, contains a suitable dose of Bonjean's ergotin, and is a rational as well as an effective

uterine styptic, exerting its influence from within, gradually and very often permanently. The latter is quite similar save that it is still broader in its utero-tonic influence due to the addition of pituitary gland (total). Both these formulas, Nos. 39 and 40, are recommended in menorrhagia, especially at or near the menopause, whether complicated by fibroids or not.

The Influence upon Fibroid Tumors. More than 20 years ago Robert Bell, of London, discovered that mammary extract exerted an influence upon uterine fibromata which caused a reduction or cure of the menorrhagia and a recession in their size. Feodoroff, of Petrograd, wrote many reports on the subject and enthusiastically advocates this treatment. As a matter of fact, reports enumerating more than a hundred cases in all might be collected from the literature extolling mammary extract as a curative remedy for this condition. I have not had much personal success in half a dozen cases personally treated, but I have seen cases that responded to the same method, while a number of physicians have written to me or told of indubitably good results. I prefer not to urge mammary preparations as a means of remedying fibroids but rather to recommend their use in the functional conditions such as show themselves in menorrhagia, etc., but I will not deny that there are possibilities that if this treatment, preferably perhaps the *Caps. Mamma-Pituitary Co.* is used to control the hemorrhagic feature of the fibroid syndrome, besides the expected benefit to the menorrhagia there may be a very pleasing reduction in the size of the tumor. Briggs, of Sacramento, is a more recent writer on this subject (*Calif. State Jour. Med.*, Sept., 1917). He reports his experiences which were quite encouraging and believes that the mammary hormone probably antagonizes the uterine stromal hormone thereby modifying or preventing excessive hyperemia thus controlling menorrhagia and the local nutrition of the uterine tissue (fibroid). The effective dosage depends on the degree of hyperovarism. As this is in preparation, I learn from a physician in Mexico that the above formula has been used by him for six months in a woman with an "inoperable fibroid" with hemorrhages, malnutrition, and a heart which precluded surgery. He writes: "The excessive flow has been entirely controlled, the patient is better in every way and the fibroid is reduced fully one half."

The Administration of Mammary Products. It will be recalled that a step-ladder method is recommended for the use of ovarian preparations (see Chapter 3 of this Section), and I will advise a modification of it for the use of any of the three mammary formulas No. 38, 39 and 40. The average dose is one capsule, occasionally two, three times a day, ordinarily just before meals. This is increased a few days before the expected flow and the dose *continued through the entire flow* and omitted thereafter for perhaps a week or longer, depending upon circum-

stances, and repeated for several months, always pushing the dosage just prior to and during the flow and resting for a while immediately after.

SECTION V. CHAPTER 15

STARLING'S "ALIMENTARY HORMONE"– SECRETIN

In 1902, Prof. E. H. Starling, of University College, London, announced the discovery of what has been called "the original hormone." He named it *secretin* and established the fact that its essential function was to activate the pancreatic enzyme precursors. It appears that this was the first internal secretory product to be studied in an accurate manner, and Starling coined the term *"hormone"* (from the Greek, "I arouse, or set in motion") to designate the class of "chemical messengers" of which the newly discovered secretin was the type.

Secretin is produced in the cells of the duodenal mucosa, and unlike the duodenal secretion is passed into the blood rather than into the alimentary canal, and by humoral passages reaches the pancreatic cells and there combines with protrypsinogen and other half-formed enzymes. The secretin becomes an actual part of the finished cell product. It is a true hormone, and in the past eighteen years has been shown to have a much larger range of physiological activity, as well as to be an agent of considerable therapeutic merit in furthering deficient functions of the character that this hormone is known to activate.

Much criticism fell upon Starling and his co-workers, especially by the Russian school headed by Popielski, who felt that the grandeur of the then recent work of Pavloff on the "appetite reflex" had been unwarrantedly dimmed. As a matter of fact, Popielski failed to show that there were any nervous impressions involved in the hormonic effects of secretin, and some years later Hustin, of Brussels, clinched the matter beyond all peradventure by activating the production of pancreatic juice by a pancreas lying in a paraffin bath, the dog having been destroyed previously. I, myself know this beyond doubt, for I had a chance to work with Hustin in his laboratory at the Institut Parc Leopold, while a method of proving the activity of secretin on the isolated pancreas was being developed.

Hallion and Enriquez, of Paris, showed conclusively that secretin-bearing extracts from the duodenum stimulated the duodenum itself to greater secretin production, as well as its other functions. The administration of secretin causes an in-

creased blood supply to the duodenal mucosa and actually increases the secretin content of the cells by test.

The Therapeutic Value of Secretin. Still later, Beveridge of New York, showed that secretin exerted a subtle influence, direct or indirect, upon the protein-digesting capacity of the blood cells, and emphasized the value of secretin-bearing extracts when given by mouth. Secretin has since been found to have an extended influence upon alimentary functions as a whole and particularly upon the liver. It was proved that duodenal extracts exert a chologogue influence equally with bile, but in a different manner. Perhaps the most recent work on this subject is that of Eddy, of Montreal (*Am. Jour. Physiol.*, March, 1919). He and Downs conclude that "the amount of bile is increased by secretin."

The subject was fully outlined by me in a paper published in the *New York Medical Journal* as far back as August, 1913, and considerable interest in the possibilities of this remedy was aroused. This article was considered of sufficient importance to be translated into German by Professor Boas, and published in his *Archiv für Verdauungs Krankheit*. In this paper, the following conclusions were made:

(1) Secretin is a specific excitant of all of the important digestive juices—pancreatic, gastric, hepatic and intestinal.

(2) It may be given by mouth with good results in the large class of gastro-hepato-intestinal disorders described under the general head of "digestive insufficiencies."

(3) Such medication is absolutely physiological, as in certain cases it seems that secretin is a necessary substance which the body is not supplying in its normal amount.

(4) Secretin is not a digestant, having no influence whatever comparable to pepsin or pancreatin.

This work has been the subject of considerable criticism, and some experimentalists have shown conclusively (upon normal or anesthetized dogs, rather than by clinical tests on patients with alimentary insufficiencies) that secretin by mouth is inactive and that dry extracts of the duodenal mucosa such as are used in medicine today do not contain secretin. Yet for nearly seven years physicians in France, Italy, England and the United States have continued the use of duodenal preparations with what they have believed to be good results—results which have showed themselves superior to those following other methods of controlling digestive deficiencies, especially in chronic cases where other measures have been tried fruitlessly.

The Physiology of Digestion. A word or two about the physiology of secretin in digestion will be helpful in establishing the importance of duodenal preparations in therapeutic practice. It is proved that the acid chyme (or HCl) passing from the stomach is the key which unlocks the duodenal cells and liber-

ates the secretin. If there is achlorhydria, obviously there is little or no secretin, and consequently pancreatic indigestion ensues, with its typical intestinal findings. If acid (lactic, hydrochloric or even tartaric) is administered to such cases in a capsule which is insoluble in the stomach, the solution of this acid in the upper intestine will partially take the place of the missing gastric acid and release some secretin, at least. In all cases of gastric insufficiency—achylia, hypopepsia, cancer (local or general) and "gastric asthenia"—the urge to liberate secretin and thereby activate the whole digestive cycle is reduced or missing.

Secretin is a stable, chemical substance which is evidently not entirely destroyed by the digestive ferments or acids, despite a few statements in the literature, hence to give it is to "set in motion" a chain of physiological circumstances of equal importance and comparatively similar to the administration of thyroid extract in hypothyroidism or any other form of homo-stimulative organotherapy. Carlson, of Chicago, denies the efficacy of secretin in therapeutics, and derides me for my opinions, yet since his paper was published I have used secretin products for three and a half years and cannot disbelieve my own experiences nor deny repeated statements made to me by other practicing physicians. One of these, a famous gastro-enterologist, whose book is well known, told me personally, after publication of the above paper with its hard and fast conclusions that my statements and those of others "run contrary to all the well established experimental facts," that he had practiced his specialty for over twenty-five years, and that he had never found as active digestive stimulants as the secretin preparations—he had used two kinds—and that he spoke from personal as well as from clinical experiences. I prefer to believe a practical clinician in anything of this character.

Clinical Reports in the Literature. There are a number of statements in the literature (and, by this time, in several of the text books) speaking favorably of the therapeutic value of duodenal extracts and secretin. Beveridge summarizes his clinical findings (*N. Y. Med. Jour.*, June 26, 1915) as follows: (1) Secretin is indicated in all pancreatic insufficiencies where true organic changes have not occurred. (2) It may be employed to advantage in aiding protein digestion. (3) It is a most important factor in raising a low urea output to normal. (4) It is indicated in gastroenterostomy and jejunostomy. (5) It is of distinct value in nephritis of intestinal origin. (6) It increases peristalsis and is indicated in all cases of stasis.

A. J. Quinby examined a number of Beveridge's patients with the X-ray and stated that the impressions of the value of this measure were gratifying. In some of the worst types of stasis, practically no iliac stasis existed and the colon delay was mate-

rially reduced. He remarked that "having followed with interest the progress of the several patients who were examined by the X-ray during their treatment with secretin, he had been pleased and astonished at the remarkable improvement" (*N. Y. Med. Jour.*, July 24, 1915, p. 217).

In the same discussion W. E. Fitch said that notwithstanding the contention of some authorities to the contrary, his personal experience had completely convinced him that secretin was a potent remedy when administered by the mouth. For about a year he had suffered from intestinal stasis, and the symptoms had been completely relieved by its use. When he stopped taking it he found that the symptoms returned, but, after taking it again for several days, these entirely disappeared. From his own experience, therefore, as well as from his observation of its effects on others, he "was an enthusiast for secretin."

With these reports, old and new, experimental and clinical, in mind, what shall we say then about the availability of duodenal extract in gastro-intestinal secretory insufficiencies, with their numerous baneful results? I say this: Secretin, i.e., suitably prepared desiccated duodenal scrapings, is well worth a trial, for it has served well heretofore and it may again!

Reinforcing Duodenal Extracts. Since the establishment of my "laboratory of applied endocrinology" I have refrained from mentioning secretin or preparing any duodenal product for sale. Time and again I have been asked why I left out of my list one of the best organotherapeutic remedies. The reason has been simply that I did not want to cause antagonism. Of course, I still believe in and use this form of organotherapy and I know that others do, and do not hesitate to say so. I have recently decided to offer a duodenal (secretin) combination and desire to say that it is indeed a helpful remedy, not merely because I feel that beneficial effects may result from its content of the duodenal principle, but for other reasons, viz: It is combined with a useful dose of active bile salts which admittedly stimulate biliary secretion, and hence are likely to be of reinforcing value in practically all forms of alimentary insufficiency for which secretin has been recommended. Further, since the adrenal glands play such an important part in the regulation of alimentary tone, both muscular and secretory, and some prominent French physicians have gone so far as to classify a definite form of indigestion as "adrenal dyspepsia" and recommend adrenal therapy for it, the addition of a suitable amount of adrenal substance is in order, the more especially as chronic digestive troubles are commonly accompanied by hypoadrenia with its cardinal symptoms of asthenia, hypotension and deficient oxidation.

Usual Indications. To conclude, I recommend *Caps. Secretin Co.* (No. 15) as an adjunct to the usual eliminative, dietetic and hygienic treatment of alimentary insufficiency, which manifest

themselves as dyspepsia; gastro-intestinal fermentation and putrefaction; hepato-biliary, pancreatic and intestinal indigestion; constipation; stasis and chronic malnutrition of digestive origin. The dosage is somewhat indefinite. In most cases, two capsules between meals suffices, and this is recommended to begin with. After two or three weeks, it may be reduced. Occasionally still larger doses may be used for a short time. It must be remembered that this is not a ferment preparation and its ingredients do not act locally upon the mucous membrane of the digestive tract and that its principal function is to facilitate the re-establishment of a deficient secretory function just as we expect glandular stimulation from any other phase of organotherapy. In whatever dose it may be given, it should be remembered that associated treatment is indicated, i.e., that *Caps. Secretin Co.* does not take the place of dietetic regulation, alkalinization, the removal of accumulated alimentary wastes, etc., and further, that the effect of this, as of other forms of organotherapy, is of a re-educative character, hence should be continued for some time.

SECTION V. CHAPTER 16

THE MINERAL SALTS IN HEALTH AND DISEASE: REMINERALIZATION

The metabolism of the mineral salts is at once one of the most difficult puzzles and one of the most fascinating studies in human physiology and has been the subject of much discussion for many years.

The mineral part of the body, as of the food, is fully as important in the nutritive process as the other better known elements. The minerals used by the body are by no means merely concerned in maintaining the cell structure, especially of the bones, but investigation of the methods whereby the body renews itself and antagonizes the toxemia of health and disease discloses a phase of mineral metabolism represented by a continued struggle betwen acids and alkalies. "Acidity spells death—alkalinity life," for after death the alkaline reaction of the blood and body fluids is lost, while on the other hand alkalies very often serve to stave off the tendency to acidemia, which is one of the grim reaper's most effective weapons.

Crystalloids and Colloids. The essential role of the inorganic elements of the body is not fully understood and much discussion has centered around the "crystalloids"—salts of an inorganic and non-physiologic character which pass rapidly

through membranes and therefore are not easily retained by the body—and the "colloids"—mineral salts which have been so changed that they have acquired an organic character and are not now crystalline but semigelatinous and diffusible. It appears that the normal salts in solution in the fluids of the body are identical *chemically* with similar inorganic salts of like molecular makeup, yet *physically* they are different, the permeability just mentioned causing a difference which enables the body to use and retain colloidal salts without their being carried off by the emunctories while the crystalline salts are speedily dissolved and eliminated. How the crystalloids metamorphose into colloids and what the difference is between, say, the potash salts in vegetables and potash dug out of the earth is not known.

In certain diseases there develops a tendency toward mineral starvation—"demineralization," as the French call it—and in tuberculosis, perhaps the best understood of these, Robin has shown that the tissues seriously lack these minerals (lime, phosphates, etc.) and also that the urinary output of these substances is greater than normal. In certain endocrine disorders (of the ovaries, parathyroids and thymus, to mention those most studied and discussed in the literature) serious changes in the mineral metabolism result and the administration of certain salts, notably of calcium, may be of noteworthy therapeutic benefit.

Bayle, of Cannes, believes that the spleen has a "colloidogenic" function—that of transforming easily lost crystalline salts into colloids which can be retained, and the prevention of a pathological change of the colloids with their subsequent automatic loss to the organism. He has given spleen extract on this basis and asserts, from the nutritional standpoint as well as from laboratory experiments, that whether his "colloidogenic theory" is sound or not, it works in practice.

The Importance of the Alkaline Reserve. Much controversy has developed over the question of the availability of the mineral organic salts so often prescribed, and, as usual, certain laboratorians seem to deny the right of the clinicians to draw their conclusions. While opinions still differ exceedingly as to the acceptability of these salts by the body, clinical experience indicates several important points which may be reiterated here:

First, the normal and abnormal wastes of the organism are either actual acids (such as lactic, carnic, indol-acetic, oxybutyric, etc.) or of an acid nature (as indican or potassium indoxyl-sulphonate)—and they combine with and neutralize the alkalies of the blood and tissues. They are "alkali robbers" and seem to make no distinction betwen the alkalies, whether colloid or crystalloid. It is well known that a certain reserve of alkaline salts is necessary to normal physiology and that among many functions which might be mentioned, the oxygen and carbon dioxide exchange carried on through the hemoglobin molecules

of the red blood cells is only accomplished effectively in the presence of an optimal amount of alkali in the blood. Decrease this reserve and oxidation becomes materially reduced, more wastes are produced throughout the body, and a vicious circle is immediately formed.

The body is continually fighting acids. Acidosis, or acidemia, are conditions which may ensue at any time that the alkali reserve is too greatly depleted, and, unfortunately, the tendency is gradually towards acidosis for "man begins to die as soon as he is born." Ordinarily the balance is well maintained in health, though the tendencies of eating, breathing and living in our "foolish civilization" are decidedly in favor of the acid state. We eat large quantities of acid-containing and acid-producing foods, especially the meats; we cook our vegetables in such a manner that the salts are lost, and we throw away the best mineral-containing portions of the cereals in our bread, and our methods of breathing and daily hygiene, all the time, favor the depletion of the all important alkaline mineral reserve. In a study of scurvy (*Jour. Biol. Chem.*, Nov., 1918), Pitz reports a number of experiments on the influence of meat and various salts upon the development of this serious nutritive disorder, and in his summary he remarks that "these experiments point to a little-emphasized role of the calcium salts in nutrition, namely, that of controlling the permeability of various animal tissues and thereby affording protection against invading agents." In this connection, some recent conclusions of Bulman, a Mexican physician (*Gaceta Acad. Med.*, Mexico, June, 1917), based upon the study of lime in physiology and therapeutics, are very interesting. The Indians in Mexico are noted for the preservation of their teeth, even in individuals of advanced age. As soon as they become "civilized" and change their dietetic habits, they develop caries, which is explained by Bulman by the loss of the phosphates and other salts found in the outer part of the grain, which is lost by the fine bolting of the flour. These are needed to keep the teeth strong, especially during pregnancy. This lack of earthy phosphates may result in disease or loss of the teeth. Incidentally, Bulman advises the addition of these salts to the food especially during pregnancy and lactation, and tells of one sick mother taking them with rickets in her child disappearing under it. The "deficiency diseases," so called, are not by any means due to a lack of vitamines but involve the whole of this question of demineralization and remineralization.

We know how common acidosis is, or, as we may now call it, demineralization. It is a serious outcome of diabetes and nephritis. It very commonly follows anesthesia, much research in the last few years indicating that the capacity of the plasma for combining with carbon dioxide is decreased by anesthesia, in other words, anesthesia depletes the alkaline reserve. As a

result of this, a generous administration of alkali prior to surgical operations prevents this depletion, increases the factor of safety, and almost entirely eliminates post-operative vomiting—a condition which we now know to be due really to demineralization. Certain metabolic disorders of children, notably rickets, epilepsy, chorea and general malnutrition, are related so intimately to mineral deficiency that cases of all of these conditions are on record as having been entirely cured by reestablishing the mineral balance. All of the chronic toxemias, including intestinal stasis, rheumatism, neurasthenia and tuberculosis, to mention a few, have a very large factor of this character, and alkaline depletion, demineralization, lime starvation, or acidosis, as this condition is variously called, is always an important factor in this condition, and evidently is a factor which can be readily and effectively modified.

The Mineral Metabolism and the Internal Secretions. Finally, mineral metabolism is intimately connected with disturbance of function of the glands of internal secretion. Not merely does dysfunction of certain glands seem to cause serious changes in the mineral balance, but since these glands as a whole maintain the tonicity, metabolism and general cellular activity of the body, insufficient endocrine function must necessarily mean a serious change in the alkali reserve. As a matter of fact, this phase of the subject has interested me unusually for one of the most common associated findings in endocrine disease is demineralization. *Dyscrinism*—deranged endocrine activity—*and demineralization*—depletion of the alkali reserve of the body—*always go together.* When one is obvious, look for the other. When organotherapy is indicated as a means of modifying disturbed endocrine activity, remineralization is distinctly in order. Take as an example the condition of hypothyroidism, one of the most frequent internal secretory disturbances. The first function of the thyroid is to stimulate oxidation, and the first result of thyroid insufficiency is deficient cell chemistry, poor oxidation and infiltration by the accumulated wastes of the organism. Since these wastes are of an acid nature, we would expect the alkali reserve of the body to be depleted and this is indeed the case, hence every case legitimately in need of thyroid extract is suffering from mineral starvation. To recapitulate: hypothyroidism means suboxidation; suboxidation means toxemia; toxemia means acidemia; acidemia means alkaline neutralization or demineralization.

Just as sure as the chemistry of the body is disturbed, either by the administration of an abnormal amount of toxins or by the production of an abnormal amount of waste products, so sure does this matter of demineralization and remineralization enter into the case, and I have yet to see an endocrine case in which this principle was not prominently involved.

Therapeutic Deductions. What is the therapeutic value of all this? It is possible to remineralize by the simple use of inorganic crystalloid salts which the organism is not supposed to be capable of "fixing" or changing to the colloid state, especially in disease as a result of which it fails to retain its own essential mineral elements? This is a difficult question to answer in a scientific manner, *but clinically it is easy.* While it may be easier to prevent demineralization of suitable quantities of selected mineral salts is helpful in several ways: (1) They neutralize excesses of acid wastes and "one cannot bring about remineralization if there exists in the organism a permanent building up of acids." (2) They thereby spare the organism, or the colloid minerals already in the body or the food ingested, for whether colloid or crystalloid, these alkaline salts immediately and inevitably must combine with these acids. (3) They indirectly favor the work of the detoxicating mechanism of the body, especially that of the ductless glands, by the restoration of the alkali reserve just mentioned. (4) They may indeed be transformed and thereby suited to be stored as the body's reserve through the colloidogenic function claimed by Bayle to lie in the spleen, as already mentioned.

At all events, the administration of "inert" organic mineral salts is not without obvious clinical benefit, whether we can answer the questions as to how this is accomplished or not. The correction of this ultimate condition is just as rational as the augmentation of the endocrine deficiency which may have caused it. Remineralization should be the rule in all chronic diseases, especially those which involve metabolism and nutrition. Several methods are available. It is very easy to recommend a package of "Arm and Hammer" brand and to suggest 60 to 100 grains a day in plenty of water, remote from meals. As a matter of fact, half a dozen generous doses of soda bicarbonate with plenty of water is now a routine preparatory measure in many surgical clinics. In France, they use bone dust, oyster shell powder and other "organotherapeutic" mineral preparations. I do not believe that these salts are any the more easily assimilated than the ordinary chemicals of commerce. For instance, dibasic calcium phosphate is actually made from bone ash and therefore, according to some, should really be called an "organic" mineral salt.

A Remineralizing Formula. For some time I have used and recommended a mixture of salts which are combined in proportions quite similar to those in the blood. This combination of salts is as follows: Magnesium phosphate, 1; dibasic calcium phosphate, 4; calcium glycerophosphate, 4; potassium bicarbonate, 16; sodium bicarbonate, 25; and sodium chloride to make 100 parts. These correspond quite closely to those found in the blood, though the more strenuous sodium carbonate is re-

placed by the bicarbonate, which is not so irritable nor is it so deliquescent. This combination, under the name Calcium-Phosphorus Co., is the standard diluent in my laboratory, taking the place of the usual milk sugar because it has a distinct therapeutic value, especially in cases where it may be advisable to use organotherapy.

To satisfy a demand which has developed quite naturally, I have prepared for me a tablet consisting of the above formula without the sodium chloride and under the name No. 11, *Tabs. Calcium-Phosphorus Co.*, each containing one gram (15½ grains), so these salts are now obtainable in convenient form, and offer an effective method of remineralization. Under ordinary circumstances, to an adult one should prescribe three tablets, crushed, with much water (2 glasses is preferable), an hour before food, twice a day. Obviously, such salts should not be taken on a full stomach for the gastric acidity would be partially neutralized and the effectiveness of the alkalies immediately lost. Two doses are more convenient than three, and fully as satisfactory, because of the difficulty of fitting them into the daily routine. Such dosage should be continued for several weeks and later renewed for a week or so each month.

The Fundamentals Emphasized. To recapitulate: I firmly believe that a concerted effort needs to be made to study the mineral balance and re-establish it, just as I have long since urged the study and regulation of the hormone balance. This is best accomplished as follows:

(1) Restore endocrine activity, i. e., support depleted adrenals, replace the missing thyroid secretion, etc., by organotherapy.

(2) Proscribe all foods which tend to produce acids. These need not be named in order to save time and controversy!

(3) Prevent alimentary stasis and toxemia, for the products of intestinal putrefaction are the most prolific sources of alkali starvation.

(4) Increase the general metabolism by exercise, water drinking and hygiene, thereby preventing the accumulation of intracellular wastes which, like all such metabolites, are bound to "steal" a certain amount of the precious reserve.

(5) Impress the importance of the alkaline value of vegetables and the acid value of meats. Potatoes are as rich in potassium salts as any available food. Remember that the usual methods of cooking dissolve out these very salts—therefore baked or steamed potatoes are far superior to boiled. Remember too that the absurd notions about the looks of flour and bread have developed a custom of removing from wheat a large portion of the salts which the Creator intended to be used and which are found in whole wheat and whole grain preparations.

(6) Administer suitable quantities of the salts which corre-

spond to those present in the blood, preferably, from my personal standpoint, as No. 11, *Tabs. Calcium-Phosporus Co.*

What results can be expected from the association of the remineralizing process with other indicated treatment? Just these, that oxidation is increased, elimination improved and the well-being very decidedly benefited. It seems superfluous to need to tell what kind of results may be expected for if a person is demineralized, he needs remineralization just as a starving person needs food; and these minerals are *indeed* foods and not drugs. This routine in our study and treatment of cellular laziness and toxemia is but one single factor. To remedy it is but *a part* of the treatment, but it is indeed an important part.

SECTION V. CHAPTER 17

ORGANOTHERAPY IN ASTHMA

The symptoms of asthma have some similarity to those connected with endocrine disturbance, and for some years it has been shown that the distressing paroxysms usually can be promptly controlled by injections of from 3 to 10 minims of adrenalin chloride solution, 1:1000. Unfortunately, the effects are ephemeral, and sometimes an effective dose of adrenalin causes a temporary vasomotor spasm which is quite uncomfortable. More recently there have been a number of reports referring to a combination of the adrenal and posterior pituitary solutions by hypodermic injection instead of adrenalin alone, and it is believed that the effects of this combination are more far-reaching and lasting. It is well known that such treatment is only symptomatic and, of course, it is inconvenient, and quite a number of physicians have presumed that the prolonged administration of some of the products of this character by mouth might be successful likewise. The subject is still in the experimental stage, and it is hard to say anything very definite about it.

The Endocrine Aspect of Asthma. Selfridge, of San Francisco, has been working on this subject for some years and recently published an article in the *California State Journal of Medicine* (April and May, 1919), reporting the endocrine findings in a number of cases of asthma. These seem to indicate that dyscrinism is an underlying, causative factor and that the control of disorders of this kind simultaneously may favor the control of the asthmatic attacks. Selfridge concludes his paper with some remarks worth quoting here: "The question of the ductless glands has been brought forward because we cannot see all cases, belonging to the different groups mentioned, cured en-

tirely by the removal of focal infections plus the injection of various protein solutions. And, while we admit that very many cases may not be benefited by the administration of gland products by mouth, especially in adults, we feel that the recognition of gland deficiency among children particularly, who exhibit vasomotor ataxia and in whom these suggestions as to treatment are followed out, may ultimately enable us to put into the class of cured cases those who otherwise might be doomed to grow up as defectives."

Anterior Pituitary Substance in Bronchial Asthma. A series of clinical experiments which may be of much practical value were recently carried out by Warfel in the Indianapolis City Hospital (*Indianapolis Med. Jour.*, July, 1915) to investigate the possibilities of organotherapy in bronchial asthma. While the administration of anterior pituitary substance in this condition was and still is empirical, it is well known that this extract has encouraging results in certain developmental disorders and irregularities of metabolism in which the endocrine organs are concerned.

Since the paroxysms of asthma are frequently controlled in a remarkable manner by injections of adrenalin, Warfel wondered if there might not be a definite hypoadrenia which could be modified by organotherapy. He proposed to do this by recourse to one of the peculiar phases of organotherapy—the use of extracts from an organ or organs which indirectly increase the physiologic activities of a hormone-producing organ which is in intimate relation to the organs from which the extracts are made. Incidentally it might be remarked that adrenal insufficiency is frequently benefited by certain glandular extracts or combinations of extracts other than adrenal substance itself.

Warfel selected seven cases of bronchial asthma, as nearly typical as possible, and to each gave 2½ grains of the desiccated anterior lobe substance four times a day. His article contains a report of each of these cases and the conclusions drawn seem to indicate that his treatment offers much encouragement in the control of a condition which is not easily influenced by other therapeutic procedures. He reports that each case thus treated showed a marked improvement in the prominent symptoms within 48 hours. The treatment was continued for periods ranging from ten days to seven weeks, with most encouraging results. The expectoration was decreased, a circumstance which was accompanied by a feeling of dryness in the mouth and throat which, however, was relieved by sipping water. The distressing dyspnea disappeared entirely. In two of the seven cases there was a considerable trace of albumin in the urine which disappeared after the treatment had been continued for a short time. The blood pressure did not seem to be influenced either up or down; and Warfel, while admitting that the number of cases was limited,

suggests that as the results secured in this series were so generally favorable and constant, further trials of this procedure are desirable in other similar cases. Since the publication of his first report, many additional cases of bronchial asthma have been treated as outlined above, with good results. It seems to be a measure worth trying still further.

The Complexity of the Asthmatic Syndrome. The trouble with the problem of the asthmatic is due to the fact that bronchial asthma is a very complex condition. There is an undoubted endocrine factor in many cases, but too often there is a bronchitis with absorption of the products of bacterial growth and decomposition with an anaphylaxis-like reaction to these foreign proteids. Again, similar reactions occurring in unusually sensitive persons following the absorption of protein from pollens and other similar substances—hay fever, horse asthma, rose colds and such like—are a few of the manifestations of this character which complicate matters.

The majority of individuals suffering from bronchial asthma are asthenic, and there are not a few references in the literature to the value of adrenal substance in cases of this kind; it might, therefore, properly be included with anterior pituitary substance in an antiasthmatic pluriglandular formula. Based upon these scattered notions, a number of experimental formulas have been made and used in different kinds of asthma with varying results. In fact, in some instances the results were very good, while in others they were negative.

A number of suggestions along these lines have been carried out in this laboratory, and a special formula (No. 26), *Caps. Adeno-Hypophysis Co.*, is offered for use in the various phases of asthma in which the effects likely to be secured from a formula of this kind possibly might be of adjuvant value in the treatment.

There are several suggestions in the literature that calcium lactate has been beneficial in certain asthmatic states and this salt is therefore used in the excipient.

Since bronchial asthma, especially in elderly persons, is such a heart-breaking condition and so unresponsive to ordinary treatment, save only the hypodermic injections which most asthmatics soon come to dread, it really seems as though experimental glandular feeding should be more routinely suggested. While there is no way of telling in advance what sort of a result may be secured, it may be stated definitely that the administration of the average doses of these glands is without harm, and on an entirely different basis from the continued injections of the adrenal or pituitary principles.

The administration of *Caps. Adreno-Hypophysis Co.* should be carried out with a full understanding on the part of the patient that it may or may not be of service. We can speak

with confidence of the value of the adrenal support obtained from that particular ingredient, and this, of course, is worth while. We can tell what others have said and of results that have been secured, but the subject is being discussed here with some diffidence merely because there is so much yet to be learned. The dose recommended is from three to six capsules a day, and obviously every effort should be made simultaneously either to control any infective condition that may be present or to have the patient keep away from foods and conditions which are known to be aggravating. A reduction of the amount of animal proteids that are eaten and persistent colon hygiene invariably should be recommended.

It will be a pleasure to cooperate with interested physicians who may have some ideas regarding the development of our present knowledge of asthma from the endocrine standpoint; and it should be remembered that my laboratory was established for the express purpose of broadening practical clinical information by making a given idea immediately utilizable, where this is possible.

SECTION V. CHAPTER 18

PLURIGLANDULAR THERAPY IN FUNCTIONAL NEUROSES

A neurosis is said to be a disorder of the nervous system not dependable on any discoverable lesion; and since there is no obvious organic change, it is natural to presume that practically all neuroses are of the functional type. There are a number of neuroses that enter into and complicate the work of the general practitioner in a most disconcerting way and involve the treatment of many cases very decidedly. Perhaps the most common of these is known as the "fatigue neurosis," a neurotic condition due to nerve tire, otherwise known as neurasthenia or psychasthenia. The subject of asthenia already has been given considerable attention in this book, and I hope it has been shown to be connected with adrenal dysfunction; for neurasthenia is likely to be profitably considered from the standpoint of the internal secretory organs, and particularly the adrenals.

Butler's Notions about Functional Diseases. An interesting statement by Dr. George F. Butler (*Am. Jour. Clin. Med.*, 1918, p. 679) may be quoted here: "The peculiar characteristic thing about the physiologic pathology of all the functional nervous diseases is that the neurons themselves are not primarily at fault. They are merely scapegoats. They bear the brunt of

some other morbid condition, and the nervous disturbance is an end-result. A quality that is common to them all is a certain irritability and spasm, due to a positive exaggeration of function, but to a sort of negative disability. The neurons may be likened to a workman fretting because of a lack or poor quality of tools; and one might as well expect to get good work out of the workman in such a plight by drugging him into stupefaction as to expect to remedy the neuroses with narcotics. Then merely add one form of toxicosis to another. The essential morbid state in all of these diseases is that of a nervous revenue which is not adequate to the ordinary demands of living. The rational principle of treatment is to bring the expenditure as far as possible within the income, either by decreasing the former or by increasing the latter, or both. In one sense they are the most obstinate of all nervous ailments, for, as intimated, these patients usually inherit their neurotic tendencies, and one has to do with the complex ramifications of biological stresses and strains. They are physical ne'er-do-wells, just as some persons are financially shiftless. It is almost as impossible to make solid, prosperous individuals out of either type as to change the leopard's spots. The most that can be done, with the physical as with the economic ne'er-do-wells, is to educate and help them to live within their modest income."

Sympatheticotonus and Vagotonus. In the last few years, two new terms have crept into current medical literature—sympatheticotonus (sympathicotonus) and vagotonus. As the names indicate, the former is a condition of tonicity resulting from overaction of the sympathetic nervous system, whereas, on the other hand, vagotonus is the result of irritability of the vagus or pneumogastric nerve. It happens that the functions of the vagus are antagonistic to those of the sympathetic; hence, vagotonus is virtually the opposite of sympatheticotonus. Both of these conditions are allied to neurasthenia and unquestionably are connected very closely with disturbances of the glands of internal secretion. In the former instance, sympatheticotonus, there is an unusual irritability of the adrenal glands with hypersensitiveness of the sympathetic and general overwork of all the organs involved and controlled by this mechanism. Naturally, sympatheticotonus will last either until it is controlled by proper therapeutics or until the organs that are played upon by the sympathetic impulses "give up," in which case the opposite manifestation, or vagotonus, will obtain.

In my estimation the whole subject of the diagnosis and treatment of these intangible nervous manifestations may be considered with greater satisfaction from the standpoint of the endocrine glands. For instance we know that the adrenal system is intimate in its control of the sympathetic nervous system; hence adrenal irritability which will cause sympatheticotonus

will also be the underlying cause of vagotonus, provided this irritation is allowed to go on far enough or until the adrenals can stand it no longer and "play out." Of course, those factors which influence the adrenal glands and, for that matter, the other glands of internal secretion, must be considered in our study of either an increase or deficiency of sympathetic tone. For example, it is well known that neuroses of this character result from fear and its twin brother, worry. In fact, nothing has done so much to establish a reasonable working basis of the cause of neurasthenia and to explain some of the remarkable results that have been secured from the treatment of conditions of this character by means of organotherapy than the work of Walter B. Cannon, at Harvard University, in which he has showed that the emotional factors so common in health and disease, including pain, hunger, fear and rage, brought about many of their ordinary physiological reactions through a direct influence upon the adrenal glands. This explains many things in our every day experience, just as it does many other things in clinical practice, especially in the functional side of neurology.

The Endocrine Aspect of the Neuroses. It is a fact that cannot reasonably be denied that most neurotic conditions are commonly associated with various endocrine disturbances. Many neurasthenics habitually complain of sensations of cold. Nervous chills are not uncommon and cold hands and feet, indefinite muscular pains and an exaggerated sense of physical exhaustion as well as mental inertia, are the rule in neurasthenia. These are also typical endocrine findings. M. Allen Starr, of New York (*Med. Record*, June 29, 1912), connects such neuroses with dysthyroidism or at least errors of the endocrine system as a whole, with more prominent manifestations in the thyroid and adrenals. He continues his description of these cases thus: "Certain neurasthenics are extremely restless and active both mentally and physically, though unable to keep their minds on one subject for any length of time. They are usually anxious about their condition, and experience a sense of heat in the body which prevents them from remaining in warm rooms. Their eyes are bright, their skin shiny and moist, their hair glossy and they are usually thin. Other typical features are tremor about the hands, exaggeration of the knee-jerks, abnormal sensations of hunger, diarrhea and excessive menses. They sleep badly, are hypersensitive to sounds and often complain of sudden flashes of heat. The pulse is often abnormally frequent, 80 to 90. In such neurasthenics as these suspicion should be awakened that there is an excess of secretion of the thyroid gland. . . ." Here the Thyroid Function Test mentioned elsewhere (Sec. IV, Chap. 4) may be of much service, for such sympathetic irritability may be of adrenal origin or, at least, not a minor form of hyperthyroidism. Treatment calculated to sedate the sympathetic

irritability simultaneously with a search for the cause with its later eradication is much more likely to be satisfactory than to ignore the endocrine element entirely—a thing which has been quite common heretofore.

Neuroses of Gonad Origin. Perhaps the most common endocrine neuroses are those associated with ovarian dysfunction, either during puberty or the menopause, or the thirty-year period in between. It is very well understood that menstrual difficulties, menopausal derangements and disturbed functional activity of the ovaries and associated organs cause neuroses of all shades, from a slight "fatigue neurosis" to a "fear neurosis" which may even metamorphose into insanity. As a matter of fact, the so-called "ovarian psychosis" is well understood as being due to disturbed ovarian activity, and many times it is amenable to treatment calculated to regulate the disturbed endocrine balance. *In other words certain insanities are cured by organotherapy.* (See especially Sec. V, Chap. 3.)

Again, the large class of sexual neuroses dependent upon overwork or abuse of the gonads may show themselves in diverse nervous, circulatory and temperamental manifestations and yet, fundamentally, be due to the original derangement of the function of these glands.

With these few points in mind, we are led to acquire an attitude in regard to the etiology, and hence to the treatment of neurotic conditions, which enables us to class them prospectively as disturbances of internal secretion, and likely to be amenable to those methods of treatment known to control disorders of this character. To recapitulate: There may be an effective organotherapy of many neuroses and psychoses.

As one prominent neurologist once said to the writer, "In so many of these indefinite nervous cases, we neurologists find ourselves up against a stone wall with no chance to scale it and about the only alternative to turn around and retrace our steps. This idea of yours (the idea is far from being my own, I have merely picked it up in my reading, and shouted about it a little louder than some of my colleagues) offers us some hope in these very cases, and I would not be surprised if the endocrines would serve as a sort of a scaling ladder to get over that terrible blank wall." This was a number of years ago, before a good many recent reports and opinions had been published on the subject, and it really seems that the vision of this neurologist is being realized and that the difficulty likened to the impossible, unscalable wall many a time is being surmounted very satisfactorily by those who are willing to consider this phase of the subject.

The principal point that I desire to make concerns the importance of a possible endocrine factor in neuroses. I do not need to quote many authorities and fit together a plexus of statements by various men prominent in the profession. The fact

remains that the endocrine aspect of the neuroses is the most encouraging of all.

Alimentary Neuroses. Toxemia and disturbed adrenal functioning react directly uopn the digestive tract. Pottenger, of Los Angeles, who has done much profitable work on the relation of the endocrines and the sympathetic system to tuberculosis, makes the following statement (*Jour. A. M. A.*, Jan. 8, 1916): "The adrenal glands are supplied through the splanchnics; and impulses which cause a general sympathetic stimulation stimulate these glands also. A minute amount of adrenin poured into the blood stream has the effect of producing a prolongation of the condition which is brought about by direct sympathetic stimulation; thus adrenin will cause a dry mouth, impaired digestion, intestinal stasis and a rapid heart. That toxemia, like the emotional states, acts by stimulating the sympathetics and by prolonging the action through the stimulation of the adrenals, seems quite certain."

Upham, of New York, in a consideration of mucous colitis (*N. Y. Med. Jour.*, Sept. 21, 1918) calls attention to the sympathetic-vagus balance in alimentary disorders as follows:

"It has been amply demonstrated that stimulation of the vagus in health produces motor activity along the gastro-intestinal canal. This activity is held in check and controlled by the inhibition from the sympathetic nervous system. The wonderful phenomenon in this occurrence is the nerve balance in the normal individual whereby stimulation is combated by just enough inhibition to produce a condition of nervous balance with resultant normal functioning of the gastro-intestinal system. But in an individual who has an over active vagus, which may be due to an excess of nerve activity of that structure, there occurs a series of spasmodic activities throughout the gastro-intestinal canal. These spasmodic activities when in the stomach produce areas of ischemia and are the foundation of deficient circulation which makes possible the location of infection from any systemic source and the production of gastric ulcer. The same series of phenomena occurs in the large intestine; a condition is brought about which gives rise to spasmodic contractions of the colon, which are a feature of the condition of mucous colitis." Here we have a plausible explanation of two phases of neurasthenia which are unusually resistant to treatment—until the endocrine aspect is appreciated.

The Search for Dyscrinism in the Neuroses. If, then, we will consider every sufferer with a functional neurosis from the standpoint of the internal secretions, we will immediately busy ourselves with finding and controlling ovarian dysfunction if it happens to be present, with the study of the patient from the standpoint of the thyroid gland, with its paramount control of detoxication and cell chemistry in general and with at least a

thought about the adrenals which are very likely to be unusually irritable or past that stage, in which case we will attempt to modify the underlying causes of this irritation, either toxic, endocrine or emotional. And if matters have reached the stage where there is a well defined adrenal insufficiency, and this is perhaps the most common single endocrine manifestation in individuals suffering with neuroses, we will establish its presence to our satisfaction by the study of the blood pressure, which will be found to be unusually low; the temperature, which is subnormal; the elimination, especially of the urinary wastes, which are usually much below par; and of the nutrition, which ordinarily is poor; and then if we can consistently make ourselves believe that a given neurasthenic patient is also suffering from hypoadrenia, we will do the next obvious thing *and treat the hypoadrenia*—not the neurasthenia. All this sounds well enough but it is "not the thing y'know," as they are wont to say in England. But if my own experience is any criterion, we will be surprised many times at the remarkable change made, not merely upon the obvious physiologic factors controlled by the adrenals and the glands associated with them but upon the patient's view of life, general health, and especially what some are pleased to call his "pep."

Again, if any other endocrine element obtrudes itself, surely the right thing to do is to go after it "hammer and tongs," and the principle that is invariably followed in all navies—clear the decks before action—is the best and only policy to follow in these particular cases. If there are disturbances of these glands in the nature of insufficiencies or otherwise, we have something to occupy ourselves with very tangibly; and since the organotherapy of endocrine disorders is altogether the most satisfactory branch of therapeutics, after we remove some underlying element which happens to be causative, before very long, in addition to reestablishing the condition toward which we are directing our treatment, we find that the neurasthenia is also responding.

The moral of this little sermon is simply this: Find an endocrine element in your neurasthenic patients and treat it, and you may be surprised at the ease with which a stubborn and intractable symptom-complex fades away.

Some Practical Therapeutic Deductions. Naturally the endocrine treatment of neuroses differs with circumstances. If there is ovarian dysfunction in the nature of an endocrine insufficiency with disturbed menses, a protracted wait between the periods, a materially reduced flow with various associated nutritional, nervous and circulatory disorders, use the formula No. 4, *Caps. Thyro-Ovarian Co.* in the expectation that physiological stimulation of not merely the ovaries but the associated endocrine glands may reestablish ovarian function and, at the same time remove a part or all of the foundation of the neurasthenia. The

same thing applies to disturbances of this character at the menopause. Here a factor to which the body has accustomed itself for many years is removed, and there is a resulting disorganization of the whole hormone balance. Mitigate this removal by adding a little to the suddenly reduced quantity of hormones and it will be found that the circulatory and nervous conditions clear up in a most remarkable fashion. On the other hand, if the ovaries seem to be irritated, the length of time between the periods is reduced, and the amount of the flow considerably increased with obvious signs of pelvic pain and discomfort, antagonize this ovarian hyperfunction by using mammary substance as represented, for example, by S. F. No. 38, *Caps. Mamma-Ovary Co.* in young women with a functional difficulty, or S. F. No. 40, *Caps. Mamma-Pituitary Co.* in older women with a heavier flow and more chronic trouble; and in addition to reducing the immediately obvious symptom—menorrhagia—the associated neurotic manifestations usually disappear with it.

The same thing applies in the male. Prostatic difficulties are very commonly associated with neurasthenia and quite frequently remedied very nicely by applying the same fundamental principles as those just mentioned; for instance, the formula S. F. No. 48, *Caps. Prostate Co.* not merely has been known to reduce local prostatic hyperesthesia and mechanical difficulties resulting from prostatic hypertrophy but to clear away at the same time the morbid neurotic state which may be dependent in a large measure upon a deranged physiology of these glands.

I have already discussed the adrenal factor in neurasthenia ("The Adrenal Glands in Health and Disease," Sec. IV, Chap. 5), and many ideas of others have been gathered together to establish the underlying importance of the adrenal glands in fatigue neuroses. The subject has been given even further consideration in a book which I published a year ago entitled, "The Adrenal Glands in Every-Day Medicine," a copy of which will be sent to interested readers as long as they last. Suffice it to say that the physician who gives to the neurasthenic with obvious hypoadrenia treatment of the ordinary character which does not include a definite effort to reestablish the disturbed endocrine function, is destined to more frequent failure than the one who believes in a treatment which includes this with all other indicated measures. This is the reason for many splendid results from the use of my *Caps. Adreno-Spermin Co.* in neuroses. The adrenal glands are supported, and functions associated with these glands are simultaneously encouraged. As a result, the low blood pressure is increased, the subnormal morning temperature is raised and with it the whole chemistry of the body, and, as a result of that, the elimination is measurably enhanced—I have seen a twenty-four hour urea figure as low as .8% and after a month's treatment found it 1.75%, whereas the normal is prob-

ably about 2%. With all these changes there ought to be a marked change for the better in the neurasthenia, which heretofore may have been treated by burdening the emunctories and paralyzing the nerve endings with bromides or allowing matters to slide by prescribing what is often erroneously called a rest or change of air.

In my brief consideration of hyperthyroidism (Sec. V, Chap. 6) it was shown that the condition known as sympatheticotonus was a typical finding, that adrenal irritability was the rule and that sympathetic sedation may be secured in cases of this type by recourse to the adreno-thyroid antagonism of the pancreas. The modification of Crotti's formula (No. 6, *Caps. Pancreas Co.*) is a useful routine remedy. The same principle applies in the treatment of the neuroses in which sympathetic irritability is a part, and the symptomatic value of this organotherapeutic sedative, especially in the functional neuroses of women at the menopause, is worthy of emphasis. The dosage of *Caps. Pancreas Co.* is from 4 to 6 a day at convenient intervals. Of course it is to be associated with attempts to find and remove underlying causes.

There is a large and growing bibliography of communications which support the position that I take in this matter. Some of these authors are convinced and obviously enthusiastic as about "a new find," while others seem to be reluctant to admit that our estimate of the etiology and treatment of the neuroses must be revised radically. We read such things as this: "All these *seem* to point to a *possible* relation between neurasthenia and . . .," etc.—and we feel justified in smiling to ourselves and recalling some patients who "seemed" to be quite pleased when they last reported.

It has been said by Tom Williams, of Washington, that the word "neurasthenia" is a cloak to cover our shortcomings in diagnosis—he is right, and I believe that this neurosis properly might be called an "endocrinosis," if such a new word is permissible.

SECTION V
APPENDIX

DOSE TABLE

	Preparation	Aver. Dose t. i. d.	Rel. Dry to Fresh	Compar. Cost *	Class
1	Adrenal (total)	½-2 gr.	1:6	2	B
2	Adrenal Cortex	2-5	1:5½	9	C
3	Adrenal Medulla	3-10 m.	1:20M	1200	A
4	Amylopsin	2-10	1:8	1.5	B
5	Bile Salts	1-5	1:40	1	A
6	Bone Medulla	1-2 dr.	...	3	B
7	Brain Substance	5	1:6	1	C
8	Corpus Luteum	2-5	1:5	10	A
9	Duodenal Scrapings	5-10	1:12	1	B
10	Hemoglobin	3-5	...	2	B
11	Kidney	5-15	1:8	2	B
12	Lecithin	½-3	...	3	B
13	Liver	5-15	1:6	1	B
14	Lung	10-20	1:10	1	C
15	Lymphatic	1-5	1:5	3	B
16	Mammary	3-10	1:4½	2	A
17	Nuclein	⅛-½	...	3	B
18	Ovary (total)	2-5	1:6½	2	A
19	Pancreas (gld.)	2-10	1:5	1	B
20	Pancreatin	2-5	1:8	1.5	A
21	Parathyroid	1/50-1/20	1:5.5	60	B
22	Parotid	2-8	1:5	1	C
23	Pepsin	3-10	...	2.5	A
24	Pineal	1/10-1/2	1:7	40	C
25	Pituitary (anterior)	1-5	1:5	7.5	B
26	Pituitary (total)	¼-1	1:4½	9	B
27	Pituitary (posterior)	1/10-1/2	1:4	15	B
28	Pituitary (post. prin.)	3-15 gt.	...	800	A
29	Placenta	3-5	1:6½	3	B
30	Prostate	3-5	1:6	3	B
31	Spermin (Leydig cells)	2-3	1:9	5	B
32	Spleen	3-10	1:4½	1	B
33	Steapsin	2-5	...	4	B
34	Submaxillary	2-5	1:8	3	C
35	Testes (orchic)	3-10	1:7½	1.5	B
36	Thromboplastin		...	4	B
37	Thymus	3-5	1:6½	2	B
38	Thyroid	1/12-1/2	1:6	2.5	A
39	Tonsil	½-1	1:7	5	C
40	Trypsin	1-5		5	A

Explanation: The dosage is in grains except where otherwise stated, and the amounts given are approximate. They may be repeated three or more times a day. The relation between a finished desiccation and the original fresh glandular parenchyma is stated as accurately as possible here, special attention is called to this as certain trade products are dosed on a basis of "fresh gland substance," obviously to the detriment of convenience and even safety. All the above doses are based upon finished products and follow the U. S. Pharmacopeia in the few instances where gland "extracts" are listed therein. The socalled "comparative cost" has been estimated approximately, and is based upon a factor called "1" which represents the cost of the less expensive desiccations such as spleen, liver, etc. The alphabetical classification is that which is discussed elsewhere in this book. Where an occasional product is not dry, as bone marrow, **thromboplastin**, "Liq. Hypophysis" (posterior principle of the pituitary) naturally no figures can be given in the fourth column.

PRICE LIST

STOCK FORMULAS

No.	NAME	INDICATION	Gr.	100
1	...ps. Adreno-Spermin Co.	Asthenia, Hypotension	v	$2.50
2	...aps. Antero-Pituitary Co.	Maldeveloped Children	v	3.75
3	...aps. Placento-Mammary Co.	Galactagogue	v	3.50
4	...Caps. Thyro-Ovarian Co.	Dysovarism, Menopause	v	3.50
5	Caps. Hepato-Splenic Co.	Trophogenic	v	3.00
6	Caps. Pancreas Co.	Hyperthyroidism	v	2.50
7	...aps. Thyroid Co. (gr. 1/8)	Hypothyroidism	v	1.75
8	...aps. Thyroid Co. (gr. 1/4)	Hypothyroidism	v	1.75
9	...Caps. Thyroid Co. (gr. 1/2)	Hypothyroidism	v	1.75
10	Thyroid Testing Capsules	Thyroid Function Test	3t	1.25
11	...bs. Calc. Phosphorus Co.	Remineralization	xv	1.50
12	...bs. Amylo-Trypsin Co.	Indigestion, Flatulence	vi	2.50
13	...s. Hemoglobin Co.	Anemia, Chlorosis, etc.	vi	3.00
14	...s. Nucleo-Lecithin Co.	Organic Phosphorus	vii	4.50
15	...s. Secretin Co.	Digestive Malsecretion	v	2.50
	...uor Hypophysis (U.S.P)	Obstetrics, Surgery, etc.		2.50

SPECIAL FORMULAS

16	T...			
	...s. Iodized Thyroid Co.	Simple Goiter	vi	...25
18	... Bile Salts Co.	Biliary Insufficiency	vi	2.50
22	... Pancreatin-Bile Co.	Intestinal Indigestion	v	3.00
23	Ca... Parathyroid Co.	Paralysis Agitans, Tetany		3.75
24	C... Adreno-Hypophysis Co.	Asthma (Exper.)		3.75
26	Cap... Thyro-Pancreas with			3.75
29	Caps... in	Hypertension (men...		3.75
30	Cap... yro-Pancreas with			
35	Caps. ...	Hypertension (wom...		
38	Cap... N... n-Hemoglobin Co.	Convalescence, Mal... nutrition		4.25
39	Caps. M... Ovary Co.	Dysovarism (Meno... hagia)		3.75
40	Caps. Mam... gotin Co.	Menorrhagia		4.00
41	Caps. ... uitary Co.	Menorrhagia (Fibro... oids)		4.25
43	Caps. Lympha... Co.	Impotence, etc.		3.75
47	Caps. Pituitary ...	Hemophilia, Lymphatism... tism		4.25
48	Caps. Prostate ...	Hypopituitarism, Infantilis... tilism		4.50
49	Caps. Placenta C...	Prost... ...ese		4.50
57	Caps. Thymus-Spe...	... ...egnancy	v	4.50
68	Caps. Spermin-Hemoglob...	... ...	vi	3. 3.75
70	Caps. Gonad C...	... ...	vi	3.5 ...50
73	Caps. Go... arian Co.	Impote...	v	...75
79	Caps. Adre... arian Co.	Amenor...	vi	5.00
82	Caps. Thy... ymphatic Co.	Asthen... ...ism		4.25
85	Caps. Renal ...	Adenoid... Lymphatis...		3.75
		Kidney Disease		3.50

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INDEX

This index combines an organotherapeutic index with a careful reference list of the numerous facts which comprise this book. It is also intended to serve as a means of facilitating the special study of the indications and value of the products of The Harrower Laboratory; and attention is called to the following statement:

The **black-faced type** is used to indicate the pluriglandular formulas of this laboratory, the stock formulas being in capitals. References to the use of these formulas are also in **black-faced type**, the first of these figures referring to the part of Section III in which a comprehensive statement concerned these preparations is made, while references to the monoglandular extracts are in ordinary type.

PERSONAL NOTES AND REFERENCES ON ORGANOTHERAPY

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